

EDITION

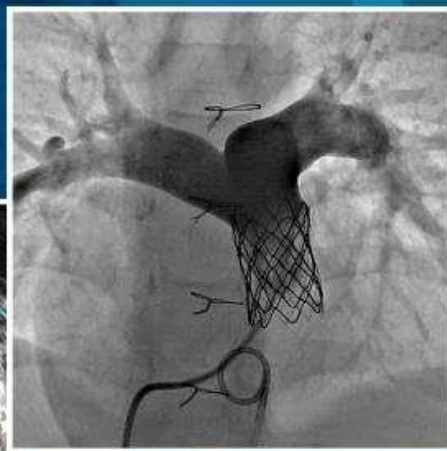
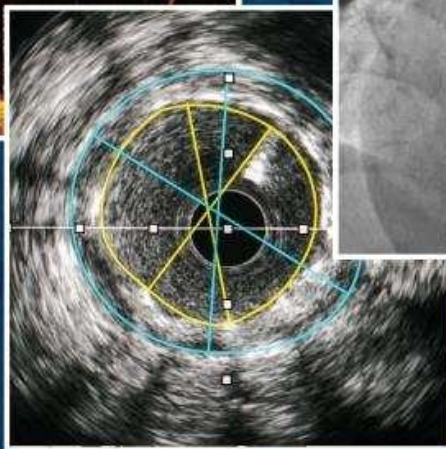
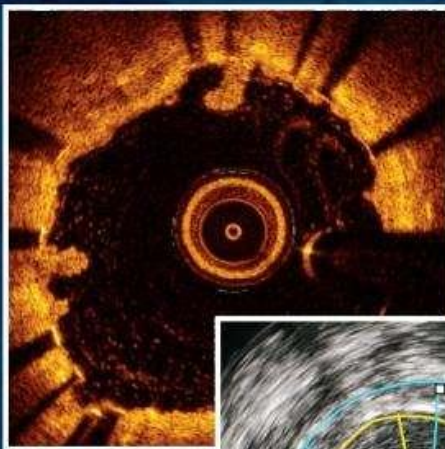
2



Enhanced
**DIGITAL
VERSION**
Included

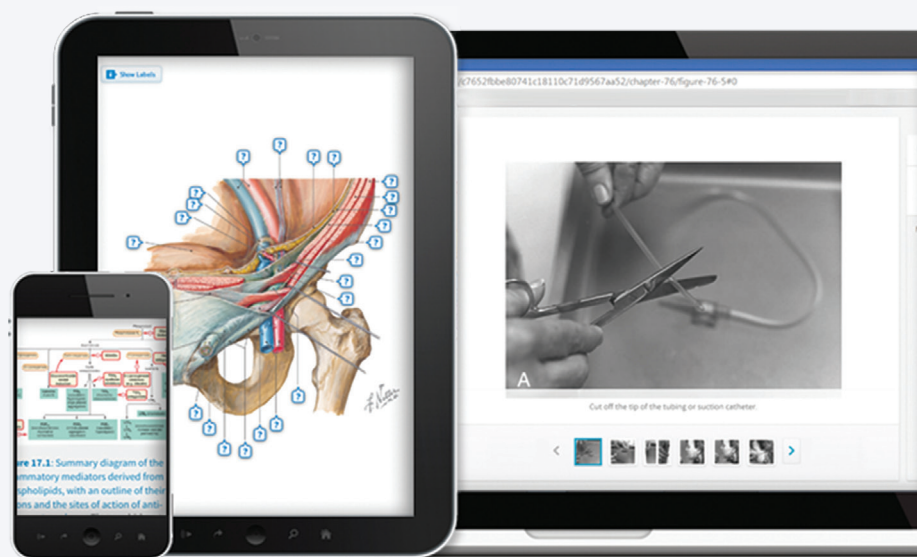
CARDIOVASCULAR INTERVENTION

A Companion to **BRAUNWALD'S**
HEART DISEASE



Any screen. Any time. Anywhere.

Activate the eBook version
of this title at no additional charge.



Elsevier eBooks+ gives you the power to browse, search, and customize your content, make notes and highlights, and have content read aloud.

Unlock your eBook today.

1. Visit <http://ebooks.health.elsevier.com/>
2. Log in or Sign up
3. Scratch box below to reveal your code
4. Type your access code into the “Redeem Access Code” box
5. Click “Redeem”

It's that easy!

For technical assistance:
email textbookscom.support@elsevier.com
call 1-800-545-2522 (inside the US)
call +44 1 865 844 640 (outside the US)

Place Peel Off
Sticker Here

Use of the current edition of the electronic version of this book (eBook) is subject to the terms of the nontransferable, limited license granted on <http://ebooks.health.elsevier.com/>. Access to the eBook is limited to the first individual who redeems the PIN, located on the inside cover of this book, at <http://ebooks.health.elsevier.com/> and may not be transferred to another party by resale, lending, or other means.

ALGrawany

2022v1.0



CARDIOVASCULAR INTERVENTION

A Companion to **BRAUNWALD'S**
HEART DISEASE

CARDIOVASCULAR INTERVENTION

A Companion to **BRAUNWALD'S**
HEART DISEASE

EDITION
2

DEEPAK L. BHATT, MD, MPH, FACC, FAHA, FESC, MSCAI

Director of Mount Sinai Heart

Dr. Valentin Fuster Professor of Cardiovascular Medicine

Icahn School of Medicine at Mount Sinai

New York, New York

United States



Elsevier
1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

CARDIOVASCULAR INTERVENTION, SECOND EDITION
Copyright © 2024 by Elsevier Inc. All rights reserved.

ISBN: 978-0-323-87368-0

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notice

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds or experiments described herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made. To the fullest extent of the law, no responsibility is assumed by Elsevier, authors, editors or contributors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Previous edition copyrighted 2016.

Content Strategist: Melanie Tucker
Content Development Specialist: Grace Onderlinde
Content Development Manager: Rebecca Gruliow
Publishing Services Manager: Shereen Jameel
Project Manager: Haritha Dharmarajan
Design Direction: Renee Duenow

Printed in India

Last digit is the print number: 9 8 7 6 5 4 3 2 1



Working together
to grow libraries in
developing countries

www.elsevier.com • www.bookaid.org

This book is dedicated, with the deepest affection and gratitude...

*To my wife, Shanthala, and our sons, Vinayak, Arjun, Ram, and Raj,
for their love and for their understanding of the many hours
I devote to patients, to procedures, and to academic pursuits*

To my parents for initially setting me on the path of a scholar

To my teachers for their knowledge, patience, wisdom, and guidance

To my patients for teaching me what matters most about being a doctor



Contributors

Tom Adriaenssens, MD, PhD

Department of Cardiovascular Sciences
KU Leuven
Department of Cardiovascular Medicine
University Hospitals Leuven
Leuven, Belgium

Shikhar Agarwal, MD, MPH, FACC

Associate
Interventional Cardiology and Structural Interventions
Geisinger Medical Center
Clinical Professor of Medicine
Geisinger Commonwealth School of Medicine
Danville, Pennsylvania

Fernando Alfonso, MD, PhD, FESC

Cardiac Department
Hospital Universitario de La Princesa
Madrid, Spain

Amjad T. AlMahameed, MD, MPH

Director
Cardiac Intensive Care
Cardiovascular Medicine
Interventional Cardiologist and Endovascular Specialist
Novant Health Presbyterian Medical Center
Charlotte, North Carolina

Saif Anwaruddin, MD

Director
Interventional Cardiology and Cardiac Catheterization
Laboratory
Cardiovascular Medicine
St. Vincent Hospital
Worcester, Massachusetts

Joe Aoun, MD

Cardiovascular Medicine
Houston Methodist Hospital
DeBakey Heart & Vascular Center
Houston, Texas

Usman Baber, MD

Director
Interventional Cardiology and the Cardiac Catheterization
Laboratory
Associate Professor of Medicine
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

Varsha Bandisode, MD

Director
Inpatient Services and Catheterization Laboratory
MUSC
Charleston, South Carolina

Subhash Banerjee, MD

Professor
Department of Medicine
UT Southwestern Medical Center
Dallas, Texas

Sripal Bangalore, MD, MHA

Professor of Medicine
Division of Cardiology
New York University School of Medicine
Director
Invasive and Interventional Cardiology
Bellevue Hospital Center
Director
Cardiovascular Outcomes Group
New York, New York

Anthony A. Bavry, MD, MPH

Professor
Department of Medicine
UT Southwestern Medical Center
Dallas, Texas

Stefan Bertog, MD, FACC, FSCAI

Department of Cardiology
CardioVascular Center
Frankfurt, Minnesota

Deepak L. Bhatt, MD, MPH, FACC, FAHA, FESC, MSCAI

Director of Mount Sinai Heart
Dr. Valentin Fuster Professor of Cardiovascular Medicine
Icahn School of Medicine at Mount Sinai
New York, New York

John A. Bittl, MD

Interventional Cardiologist
Cardiac Catheterization Laboratory
AdventHealth Ocala
Ocala, Florida

**Emmanouil S. Brilakis, MD, PhD**

Director
Center for Complex Coronary Interventions
Minneapolis Heart Institute
Minneapolis, Minnesota

Robert A. Byrne, MB BCh, PhD

Professor of Cardiovascular Research
School of Pharmacy and Biomolecular Sciences
RCSI University of Medicine and Health Sciences
Dublin, Ireland
Director of Cardiology
Mater Private Network
Dublin, Ireland

Alex Bou Chebl, MD

Professor of Neurology
Department of Neurology
University of Louisville School of Medicine
Louisville, Kentucky

Mauro Chiarito, MD

Department of Biomedical Sciences
Humanitas University
Pieve Emanuele
Milan, Italy

Antonio Colombo, MD

Senior Consultant
Department of Cardiology
Humanitas Research Hospital
Rozzano, Milan, Italy

J.J. Coughlan, MB, BCh, BAO, MD

Interventional Cardiologist
Department of Cardiology
Deutsches Herzzentrum München
Technische Universität München
Munich, Germany

George Dangas, MD, PhD

Professor
Department of Medicine (Cardiovascular Disease)
Icahn School of Medicine at Mount Sinai
New York, New York

Michele L. Esposito, MD

Assistant Professor of Medicine
Medicine
MUSC
Charleston, South Carolina

David P. Faxon, MD

Clinical Faculty
Department of Medicine
Division of Cardiology
Brigham and Women's Hospital
Senior Lecturer
Harvard Medical School
Boston, Massachusetts

Sachin S. Goel, MD

Medical Director
Structural Heart Interventions
Department of Cardiology
Houston Methodist Hospital
Houston, Texas

William A. Gray, MD

System Chief of Cardiovascular Services
Department of Medicine
Main Line Health
Wynnewood, Pennsylvania
Co-director
Lankenau Heart Institute
Main Line Health
Wynnewood, Pennsylvania
Professor of Medicine
Department of Medicine
Sidney Kimmel Medical College
Thomas Jefferson University
Philadelphia, Pennsylvania

Philippe G  n  reux, MD

Director of Structural Heart and Valve Program
Cardiology
Gagnon Cardiovascular Institute at Morristown Medical
Center
Morristown, New Jersey

Dagmara Hering, MD, PhD

Department of Hypertension and Diabetology
Medical University of Gdansk
Gdansk, Poland

Howard C. Herrmann, MD

John W. Bryfogle Jr. Professor of Cardiovascular Medicine
Department of Medicine
Cardiovascular Division
Perelman School of Medicine of the University of
Pennsylvania
Health System Director
Interventional Cardiology Program
University of Pennsylvania
Philadelphia, Pennsylvania

Pamela Iloska, MD

Cardiologist
CardioVascular Center CVC Frankfurt
Frankfurt, Germany

Ik-Kyung Jang, MD, PhD

Professor of Medicine
Department of Medicine
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Hani Jneid, MD, FACC, FAHA, FSCAI

Professor and Chief
Department of Cardiology
University of Texas Medical Branch
Galveston, Texas

Marwan F. Jumean, MD

Interventional Heart Failure Fellow
The Cardiovascular Center
Tufts Medical Center
Boston, Massachusetts

David E. Kandzari, MD

Chief
Piedmont Heart Institute and Cardiovascular Service Line
Director
Interventional Cardiology
Piedmont Heart Institute
Chief Scientific Officer
Piedmont Healthcare
Atlanta, Georgia

Samir R. Kapadia, MD

Chairman
Department of Cardiovascular Medicine
The Cleveland Clinic Foundation
Cleveland, Ohio

Navin K. Kapur, MD

Interventional Cardiologist
The Cardiovascular Center
Tufts Medical Center
Boston, Massachusetts

Adnan Kastrati, MD

Professor of Cardiology
Department of Cardiology
Deutsches Herzzentrum
Munich, Germany

Morton J. Kern, MD, MSCAI, FAHA, FACC

Professor of Medicine
Department of Cardiology
University California Irvine
Orange, California
Chief
Department of Cardiology
Long Beach Veterans Health Care System
Long Beach, California

Scott Kinlay, MBBS, PhD

Chief of Cardiology
Director Cardiac Catheterization Laboratory and Vascular
Medicine
Department of Medicine
Cardiovascular Division
VA Boston Healthcare System
West Roxbury, Massachusetts
Physician
Department of Medicine
Cardiovascular Division
Brigham and Women's Hospital
Boston, Massachusetts
Associate Professor in Medicine
Harvard Medical School
Boston, Massachusetts
Adjunct Associate Professor in Medicine
Boston University Medical School
Boston, Massachusetts

Lloyd W. Klein, MD, MSCAI, FACC

Clinical Professor of Medicine
Division of Cardiology
University of California, San Francisco
Santa Rosa, California

Susheel K. Kodali, MD

Associate Professor
Department of Medicine
Columbia University Medical Center
New York, New York

Amar Krishnaswamy, MD

Section Head
Interventional Cardiology
Cleveland Clinic
Cleveland, Ohio

Azeem Latib, MD

Section Head and Director of Interventional Cardiology
Director of Structural Heart Interventions
Interventional Cardiology
Montefiore Medical Center
New York, New York

Martin B. Leon, MD

Founder and Chairman Emeritus
Medical Research and Education Division
Cardiovascular Research Foundation
New York, New York

**Ronan Margey, MB, BAO, BCH, BMEDSCI, MSC, MRCPI, FACC, FSCAI, FACC**

Clinical Director
Mater Private Hospital Cork
Head of Cardiology
Cardiology Department
Mater Private Hospital Cork
Cork, Ireland
National Clinical Lead
Irish Heart Attack Audit
National Office of Clinical Audit
Royal College of Surgeons of Ireland
Dublin, Ireland
Senior Clinical Lecturer in Medicine
Department of Medicine
University College Cork
Cork, Ireland

Roxana Mehran, MD

Professor of Medicine (Cardiology)
Director of Interventional Cardiovascular Research and
Clinical Trials
Zena and Michael A. Wiener Cardiovascular Institute
Icahn School of Medicine at Mount Sinai
New York, New York

Aravinda Nanjundappa, MD

Director of Peripheral Interventions
Cardiovascular Medicine
Cleveland Clinic Foundation
Cleveland, Ohio

Vivian G. Ng, MD

Assistant Professor of Medicine
Department of Cardiology
Columbia University Medical Center
New York, New York

William J. Nicholson, MD

Associate Professor
Director of Interventional Cardiology
Department of Cardiology
Emory Health Care
Atlanta, Georgia

Brian O'Neill, MD

Director of Interventional and Structural Heart Research
Cardiology
Henry Ford Hospital
Detroit, Michigan

John W. Osborn, PhD

Professor
Department of Surgery
University of Minnesota
Minneapolis, Minnesota

William W. O'Neill, MD, FACC, FSCAI

Medical Director
Structural Heart Disease
Henry Ford Hospital
Detroit, Michigan

Igor F. Palacios, MD

Director of Interventional Cardiology
Division of Cardiology
Massachusetts General Hospital
Harvard Medical School, Boston
Boston, Massachusetts

Lourdes R. Prieto, MD

Director, Division of Cardiology
Chief, NCPS Section of Cardiovascular Medicine
Nicklaus Children's Hospital
Miami, Florida

Vikram Rajpurohit, MD

Assistant Professor
Radiology
NYU Langone
New York, New York

Claire E. Raphael, MD, PhD, FACC

Department of Cardiology
Cleveland Clinic
Cleveland, Ohio

Markus Reinartz, MD

CardioVascular Center CVC Frankfurt
Frankfurt, Germany

John F. Rhodes, Jr., MD

Adult Congenital Invasive Cardiology
Pediatric Cardiology Services and the Adult Congenital
Heart Program
Medical University of South Carolina
Charleston, South Carolina

Pratik Sandesara, MD

Assistant Professor of Medicine
Department of Cardiology
Emory University
Atlanta, Georgia

Nicolas W. Shammass, MD, MS, EJD, FACC, FSCAI

Adjunct Clinical Associate Professor
Internal Medicine
University of Iowa Hospitals and Clinics
Research Director and Founder
Midwest Cardiovascular Research Foundation
Consulting and Interventional Cardiologist
Cardiovascular Medicine, PC
Davenport, Iowa

**Alok Sharma, MD**

Director
Interventional and Structural Heart Research
Department of Cardiology
Minneapolis VA Medical Center
Co-Director
Structural Heart and Valve Program
Department of Cardiology
Minneapolis VA Medical Center
Site Director
Interventional and Structural Heart Fellowship Program
Minneapolis VA Medical Center
Minneapolis, Minnesota

Horst Sievert, MD, PhD

Director
CardioVascular Center Frankfurt CVC
Frankfurt, Germany

Kolja Sievert, MD

Physician
Cardiology
CVC Frankfurt
Frankfurt, Germany

Akhilesh K. Sista, MD

Assistant Professor of Radiology
Weill Cornell Medical College
New York, New York

Gregg W. Stone, MD

Director of Academic Affairs
Department of Cardiology
Mount Sinai Heart
New York, New York

E. Murat Tuzcu, MD, FACC

Vice Chair for Clinical Operations
Cardiovascular Medicine
Cleveland Clinic
Cleveland, Ohio

Suresh Vedantham, MD

Professor of Radiology and Surgery
Mallinckrodt Institute of Radiology
Washington University School of Medicine
St. Louis, Missouri

Christopher J. White, MD

Professor and Chair
Department of Medicine and Cardiology
Ochsner Clinical School, Univ Queensland
Medical Director
Centers of Excellence and Service Lines
Ochsner Medical Center
Medical Director
Value Based Care
Ochsner Health
New Orleans, Louisiana

David O. Williams, MD

Professor of Medicine
Harvard Medical School
Senior Physician
Cardiovascular Division
Brigham and Women's Hospital
Boston, Massachusetts

James B. Young, MD

Professor of Medicine
Lerner College of Medicine of Case Western Reserve
University
Executive Director for Academic Affairs
Cleveland Clinic
Cleveland, Ohio

Khaled M. Ziada, MD, FACC, FSCAI

Chief Academic Officer
Cardiovascular Medicine
Cleveland Clinic
Cleveland, Ohio



Foreword

Interventional cardiology is a robust subspecialty, with its own subspecialty board, training programs, journals, and international meetings. Although grounded in conventional cardiology, it interfaces with radiology, cardiac and vascular surgery, and pediatrics and neurology as well. As a consequence, the lines that previously separated cardiology from these other disciplines are becoming blurred.

Dr. Deepak L. Bhatt brilliantly edited the first edition of *Cardiovascular Intervention*, a key companion to *Heart Disease*. Not surprising, it was well received. Also not surprising, the field has moved forward rapidly in the past 7 years. Therefore, building on the success of the first edition, Dr. Bhatt has led the preparation of this new second edition of *Cardiovascular Interventions*. In addition to its focus on coronary interventions, it deals with important interventions in structural heart disease, including congenital heart disease, valvular heart disease, and advanced heart failure, as well as diseases of the aorta and various systemic arterial beds. Between the first edition and the present one, much has changed. For example, the approaches to left main bifurcations and chronic total occlusions are now completely different. Whereas transcatheter aortic valve replacement has achieved a certain degree of maturity, transcatheter mitral and tricuspid valve interventions are just getting started.

Dr. Bhatt brings a wealth of personal experience to this task. As a practicing interventional cardiologist, he faces the clinical problems that are discussed in this book on a regular basis. He is also an experienced clinical trialist, which provides him with the ability to assess the validity of the myriad studies published in this field.

Dr. Bhatt has again assembled a group of talented, experienced authors to prepare *Cardiovascular Intervention*. The book is well illustrated and contains 176 videos, 506 figures, and 128 tables, which summarize an enormous amount of material. It is as up to date as this month's journals and meetings. This text offers great value to both trainees and practitioners in this important field, as well as to radiologists, cardiovascular surgeons, and general cardiologists who interact frequently with interventional cardiologists.

We are proud to include this new edition of *Cardiovascular Intervention* in the family of updated companions to *Braunwald's Heart Disease*.

Eugene Braunwald
Peter Libby
Robert O. Bonow
Douglas L. Mann
Gordon F. Tomaselli
Scott D. Solomon



Preface

Cardiovascular intervention has saved many lives and improved quality of life. The widespread adoption of cardiovascular intervention worldwide has, in part, led to a decrease in the rate of cardiovascular death for several conditions—though in absolute terms, because of the aging of the population and increasing urbanization, the population at risk is growing, and the global cardiovascular epidemic continues.

Few areas in medicine have advanced as meaningfully and rapidly as cardiovascular intervention. The field now encompasses complex coronary intervention, peripheral arterial and venous procedures, cerebrovascular intervention, congenital heart disease, and valvular as well as other structural heart interventions. The care of patients with this panoply of diseases involves multidisciplinary teams increasingly housed in heart and vascular centers, designed around optimizing the patient experience as opposed to the silos of physician and surgeon specialties of the past.

What was previously only treatable with a scalpel can currently be approached with a catheter. This transformation of several open surgical procedures to truly minimally invasive interventional procedures has been of great benefit to patients. Additionally, this evolution potentially allows many more patients to be served even in relatively resource-poor settings and with greater cost effectiveness in all economic environments.

For decades now, innovation and intervention have gone hand in hand. Pioneers in cardiovascular intervention have boldly pushed the boundaries of what is possible. Physicians, scientists, and engineers from industry have served as valuable partners in this exciting journey. The advances in devices, pharmacotherapies, and procedural techniques would not have been possible without this collaboration. As well, the free flow of information across countries and specialties has allowed cardiovascular intervention to mature at an impressive pace for what—viewed within the larger context of medicine—is still a relatively young field.

The resulting explosion of the required knowledge base for practitioners in the field of cardiovascular intervention

has created a challenge—how to keep up! In this companion to *Braunwald's Heart Disease*, world-renowned authors provide the latest data to inform decision making in cardiovascular intervention. Furthermore, they provide details on the technical aspects of optimizing procedural care. This focus on both cognitive and procedural elements of cardiovascular intervention provides a needed resource in this dynamic field.

In joining the great lineage of the *Heart Disease* family, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*, now in its second edition, aims to provide the wide variety of health care personnel involved with cardiovascular intervention with evidence-based information critical for successfully ensuring the best possible care. It is meant as an aid to make decisions at the bedside, as a reference text for specific questions, and as a resource for scientific inquiry and investigation. Cardiovascular intervention is a very visual specialty, and this book has ample figures and abundant videos to provide this necessity. Frequent online supplements will keep the book vibrant in an era of rapid change, with the textbook portion anchoring knowledge that has stood the test of time. Electronic links to *Braunwald's Heart Disease* and other companion textbooks should make for a comprehensive, current, and visually compelling resource in cardiovascular intervention that is placed within the larger universe of cardiovascular disease care.

My dream is that interventional cardiologists, cardiac and vascular surgeons, interventional radiologists and neurologists, trainees, medical students, nurses and nurse practitioners, physician assistants, industry partners, researchers, and others involved with patients undergoing cardiovascular interventions can learn from this book, guiding them in the daily care of their patients. As such, my sincere hope is that these diverse readers find the second edition of *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease* to be a valuable educational tool that conveys the passion the authors and I feel for the beauty and grandeur of cardiovascular intervention.

Deepak L. Bhatt, MD, MPH, FACC, FAHA, FESC, MSCAI



Acknowledgments

The distinguished authors of this textbook deserve my most heartfelt appreciation. They have produced expert, comprehensive, and timely chapters of which they should be extremely proud. I would like to thank the publishing staff at Elsevier for their assistance in helping make both the content and visuals outstanding. In particular, I would like to thank Dolores Meloni (publishing director, Medical Reference and Clinics Continuity), Melanie Tucker (senior content strategist), and Grace Onderlinde (content

development specialist) for their exemplary efforts in assembling what I hope will continue to be viewed as the definitive treatise on cardiovascular intervention. I am immensely grateful to Dr. Eugene Braunwald, an inspiring and generous mentor, for having faith in me and for selecting me to serve as editor of the first and now second editions of this textbook that bears his name—a name synonymous with greatness in medicine.



Contents

SECTION I INTERVENTIONAL CARDIOLOGY

- 1 The Birth Of Interventional Cardiology, 1**
DAVID O. WILLIAMS
- 2 Guidelines And Appropriateness Criteria For Interventional Cardiology, 7**
DAVID P. FAXON
- 3 Vascular Access And Closure, 23**
SRIPAL BANGALORE
- 4 Pharmacotherapy In The Modern Interventional Suite, 56**
HANI JNEID
- 5 Hemodynamic Support During High-Risk Percutaneous Coronary Intervention, 80**
WILLIAM W. O'NEILL AND BRIAN O'NEILL P
- 6 Radiation Safety In The Cardiac Catheterization Laboratory, 102**
LLOYD W. KLEIN
- 7 Contrast Selection, 115**
MAURO CHIARITO, USMAN BABER, GEORGE DANGAS, AND ROXANA MEHRAN

SECTION II CORONARY ARTERY INTERVENTION

- 8 Percutaneous Coronary Intervention For Unprotected Left Main Coronary Artery Disease, 127**
PHILIPPE GÉNÉREUX AND GREGG W. STONE
- 9 Chronic Total Coronary Occlusions: Rationale, Techniques, And Clinical Outcomes, 159**
DAVID E. KANDZARI, PRATIK B. SANDESARA AND WILLIAM J. NICHOLSON
- 10 Bifurcations, 175**
ANTONIO COLOMBO AND AZEEM LATIB
- 11 Bypass Graft Interventions, 206**
EMMANOUIL S. BRILAKIS AND SUBHASH BANERJEE
- 12 Calcified Lesions, 222**
AMAR KRISHNASWAMY AND CLAIRE E. RAPHAEL

- 13 Treatment Of In-Stent Restenosis, 235**
J.J. COUGHLAN, ROBERT A. BYRNE, FERNANDO ALFONSO AND ADNAN KASTRATI
- 14 Management Of Thrombotic Lesions, 256**
ANTHONY A. BAVRY
- 15 Fractional Flow Reserve And Nonhyperemic Pressure Ratios, 263**
MORTON J. KERN
- 16 Intravascular Ultrasound Imaging, 290**
KHALED M. ZIADA
- 17 Optical Coherence Tomography, 319**
TOM ADRIAENSSENS, JAMES FUJIMOTO AND IK-KYUNG JANG

SECTION III PERIPHERAL ARTERY INTERVENTION

- 18 Intervention For Lower Extremity Arterial Disease, 337**
SCOTT KINLAY
- 19 Upper Extremity Intervention, 362**
AMJAD T. ALMAHAMEED
- 20 Renal Artery Intervention: Catheter-Based Therapy For Renal Artery Stenosis, 371**
CHRISTOPHER J. WHITE
- 21 Mesenteric Artery Intervention: Catheter-Based Therapy For Chronic Mesenteric Ischemia, 381**
CHRISTOPHER J. WHITE
- 22 Renal Denervation, 385**
STEFAN BERTOG, KOLJA SIEVERT, ALOK SHARMA, PAMELA ILIOSKA, MARKUS REINARTZ, DAGMARA HERING, JOHN OSBORN, AND HORST SIEVERT
- 23 Endovascular Management Of Aortic And Thoracic Aneurysms, 407**
ARAVINDA NANJUNDAPPA

SECTION IV CEREBROVASCULAR INTERVENTION

- 24 Carotid And Vertebral Intervention, 441**
WILLIAM A. GRAY
- 25 Cerebrovascular Interventions, 462**
ALEX BOU CHEBL

SECTION V **VENOUS INTERVENTION****26 Interventional Management Of Lower Extremity Deep Vein Thrombosis And Pulmonary Embolism, 479**VIKRAM RAJPUROHIT, MD, AKHILESH K. SISTA, MD,
SURESH VEDANTHAM, MD**27 Management Of Chronic Venous Insufficiency, 493**

NICOLAS W. SHAMMAS

28 Hemodialysis Access Intervention, 513

JOHN A. BITTL

SECTION VI **STRUCTURAL HEART INTERVENTION****29 Aortic Valvuloplasty And Transcatheter Aortic Valve Replacement, 521**

SUSHEEL K. KODALI, VIVIAN G. NG AND, MARTIN B. LEON

30 Transcatheter Mitral Valve Intervention, 554

SAIF ANWARUDDIN AND HOWARD C. HERRMANN

31 Transcatheter Tricuspid Valve Intervention, 573

SAIF ANWARUDDIN AND HOWARD C. HERRMANN

32 Hypertrophic Cardiomyopathy, 577

SHIKHAR AGARWAL AND E. MURAT TUZCU

33 Patent Foramen Ovale, Atrial Septal Defect, Left Atrial Appendage, And Ventricular Septal Defect Closure, 596SACHIN S. GOEL, JOE AOUN, LOURDES R. PRIETO, AND
SAMIR R. KAPADIA**34 Interventions For Advanced Heart Failure, 626**

NAVIN K. KAPUR, MICHELE L. ESPOSITO, AND MARWAN F. JUMEAN

35 Endomyocardial Biopsy, 650

JAMES B. YOUNG AND DEEPAK L. BHATT

36 Pericardiocentesis And Pericardial Intervention, 663

RONAN MARGEY AND IGOR F. PALACIOS

SECTION VII **CONGENITAL HEART DISEASE****37 Adult Congenital Heart Disease: Cardiovascular Interventions For Pulmonary Arterial Hypertension, Anomalous Vascular Connections, Aortic Coarctation, And Pulmonary Valve Replacement, 679**

JOHN F. RHODES, JR.

Index, 691



Video Contents

3 Vascular Access and Closure

- 3.1: Through-and-through puncture technique for radial artery cannulation.
- 3.2: Anterior wall puncture technique for radial artery cannulation.
- 3.3: Patent hemostasis using a TR band for radial artery hemostasis.

4 Pharmacotherapy in the Modern Interventional Suite

- 4.1: Femoral artery pseudoaneurysm in a patient treated with triple antithrombotic therapy.
- 4.2: A and B, Zenker diverticulum precluding administration of oral antiplatelet therapy before percutaneous coronary intervention.
- 4.3: A–D, Acute stent thrombosis in a patient inadequately anticoagulated with enoxaparin before percutaneous coronary intervention.
- 4.4: A and B, Coronary perforation during percutaneous coronary intervention in a patient receiving bivalirudin.
- 4.5: A and B, Catheter-induced vasospasm treated with an intracoronary vasodilator.

5 Hemodynamic Support During High-Risk Percutaneous Coronary Intervention

- 5.1: Contrast aortogram before Impella.
- 5.2: Impella inserted in the left ventricle.
- 5.3: Baseline angiogram of the left main.
- 5.4: Angiogram after rotational atherectomy of the left anterior descending coronary artery.
- 5.5: Angiogram during stent deployment in the circumflex artery.
- 5.6: Simultaneous balloon inflation in the left anterior descending coronary and circumflex arteries.
- 5.7: Final angiogram after the left main stent.
- 5.8: Removal of Impella; end of the procedure.

8 Percutaneous Coronary Intervention for Unprotected Left Main Coronary Artery Disease

- 8.1: Provisional stenting technique with final kissing.
- 8.2: Culotte technique with final kissing.
- 8.3: Crush technique with final kissing.
- 8.4: Double kissing crush technique.
- 8.5: T-stent technique (with T-stenting and small protrusion technique).
- 8.6: V stenting (double-barrel) technique.

10 Bifurcations

- 10.1: Critical stenosis of the mid left anterior descending coronary artery with minimal disease of the diagonal ostium.

10.2: Occlusion of the diagonal branch in 10.1 after stent implantation in the left anterior descending coronary artery.

10.3: Severe stenosis of the proximal left anterior descending coronary artery involving the diagonal ostium that has a hairpin bend origin.

10.4: Pullback wiring technique to wire the angulated side branch in Video 10.3.

10.5: Critical stenosis of the left main coronary artery bifurcation with minimal discrepancy between the distal left main and left circumflex coronary artery that would be suitable for culotte stenting.

10.6: Final result after culotte stenting of the bifurcation in Video 10.5.

10.7: Critical stenosis of the left anterior descending coronary artery (LAD) diagonal bifurcation with a large discrepancy between the LAD and diagonal that would not be suitable for culotte but rather for mini-crush stenting.

10.8: Final result after mini-crush stenting of the bifurcation in Video 10.7.

10.9: Left main coronary artery bifurcation with an angle between the distal left anterior descending coronary artery and the left circumflex coronary artery greater than 70 degrees that would be more suitable for culotte or T stenting.

10.10: Final result after culotte stenting of the bifurcation in Video 10.9.

10.11: Left anterior descending coronary artery (LAD) diagonal bifurcation with an angle less than 70 degrees between the distal LAD and diagonal that would not be suitable for T stenting but rather the mini-crush or culotte technique.

10.12: Final result after mini-crush stenting of the bifurcation in Video 10.11.

10.13: Medina 0.1.1 bifurcation with minimal disease in the proximal main branch that would be suitable for V stenting.

10.14: Final result after V stenting of the bifurcation in Video 10.13.

10.15: Chronic total occlusion of a left anterior descending coronary artery diagonal bifurcation.

10.16: Dissection of both branches after predilation.

10.17: Final result after double kissing mini-crush stenting of the bifurcation in Videos 10.15 and 10.16.

10.18: Right anterior oblique caudal view of severe thrombotic occlusion of the distal left main involving the proximal left anterior descending coronary artery and left circumflex coronary artery.

10.19: Cranial view of severe thrombotic occlusion of the distal left main involving the proximal left anterior descending coronary artery and left circumflex coronary artery.

10.20: Both stents were placed at the same time with the side branch stent protruding minimally into the main branch.

10.21: Angiography immediately after stent implantation confirming patency of both branches.

10.22: Spider view of final result after optimization with a two-step final kissing balloon inflation of the bifurcation in Videos 10.18 and 10.19.



10.23: Right anterior oblique caudal view of the final result after optimization with a two-step final kissing balloon inflation of the bifurcation in Videos 10.18 and 10.19.

11 Bypass Graft Interventions

11.1 and 11.2: Example of no reflow during saphenous vein graft (SVG) intervention. The target SVG had diffuse degeneration (Video 11.1). After advancement of a FilterWire through the SVG, no reflow was observed (Video 11.2), and the patient developed severe chest pain and ST-segment elevation.

11.3 and 11.4: Example of debris capture by a filter. A FilterWire was placed distally to an eccentric saphenous vein graft body lesion (Video 11.3). During percutaneous coronary intervention, debris embolized distally and was captured within the filter (Video 11.4).

11.5: Example of subclavian steal syndrome. Reversal of flow in the left internal mammary artery graft caused by severe proximal left subclavian stenosis.

12 Calcified Lesions

12.1: Severe right coronary artery (RCA) calcification for planned rotational atherectomy (video case 1). This was a 70-year-old man with a history of multiple percutaneous coronary intervention to the mid RCA and mid left anterior descending coronary artery. He declined coronary artery bypass grafting. He presented with angina and was found to have severe calcific disease of a dominant RCA. Diagnostic image of the RCA in left anterior oblique 30 before rotablation. Note the heavy calcification throughout the proximal and mid vessel. There is a stent in the mid RCA with moderate in-stent restenosis (ISR). Subsequent optical coherence tomography showed two layers of stent with neointimal hyperplasia.

12.2: Rotablation of the right coronary artery (RCA) (video case 1). A three-dimensional right guide was seated just outside the RCA ostium. A workhorse wire loaded into a microcatheter was advanced into the distal vessel, and the microcatheter was used to exchange for the Rota floppy wire. Multiple passes of a 1.5-mm ROTAPRO burr were performed. The video shows the second run of rotational atherectomy. Initially, high-speed rotation was performed at 180 rpm in a pecking motion at the lesion with care taken to advance slowly to reduce the risk of burr entrapment distal to the severe calcific lesion. Further runs at 160 rpm were then performed for further plaque modification.

12.3: Optical coherence tomography (OCT) after rotational atherectomy (RA; video case 1) After RA, we were able to advance OCT into the distal vessel. Images showed moderate in-stent restenosis (ISR) and two layers of stent within the mid right coronary artery (RCA; A, stents arrowed). The proximal lesion had severe superficial and deep calcification, and the lesion appeared well prepared after rotablation with multiple cracks and fissures (B, proximal RCA close to the ostium; C, proximal RCA within the ectatic segment proximal to old stent).

12.4: Final angiographic result (video case 1). After rotational atherectomy, a 4-mm balloon expanded well, and we prepared the lesion with a 4.0 × 20 NC balloon. We placed a 4.0 × 33 everolimus-eluting stent with good angiographic result. We post dilated with a 4.0 NC and 5.0 NC in the proximal ectatic region. Given there were two layers of stent, we opted to manage the mid right coronary artery in-stent restenosis (ISR) with medical therapy in the first instance with a plan to perform brachytherapy if the patient continued to have symptoms.

12.5: Right coronary artery (RCA) treated with orbital atherectomy (video case 2). This 77-year-old man underwent coronary artery bypass grafting in 1005 with a patent left internal mammary artery to left anterior descending coronary artery but occluded vein graft to the RCA. He was planned to have percutaneous coronary intervention to the RCA. Diagnostic

angiography in left anterior oblique 30 showed a severe calcified lesion in the proximal RCA and a further severely calcified lesion in the mid RCA.

12.6: Right coronary artery treated with orbital atherectomy (video case 2). Right anterior oblique view of the vessel.

12.7: Right coronary artery treated with orbital atherectomy (Video case 2). Using a 6F JR4 guide, we performed rotational atherectomy with a 1.25mm burr through the proximal lesion. However, the ROTAPRO would not advance through the distal lesion due to lack of guide support.

12.8: Right coronary artery treated with orbital atherectomy (video case 2). We therefore advanced a 6-Fr Guideliner for support. We performed balloon dilation with a 1.0-mm low-profile balloon, which burst, and then a 1.5-mm balloon, which also burst. We were not able to advance a 2.0 noncompliant balloon. We therefore switched to orbital atherectomy. This is compatible with a 6-Fr Guideliner (ROTAPRO is compatible with a 7-Fr but not a 6-Fr Guideliner). We exchanged for a Viper wire and performed multiple passes through the distal lesion with the 1.25-mm Diamondback orbital atherectomy system.

12.9: Right coronary artery treated with orbital atherectomy (video case 2). Because the orbital atherectomy system is bidirectional, there is less concern about burr entrapment, and plaque modification occurs both when advancing and when retracting the device.

12.10: Right coronary artery (RCA) treated with orbital atherectomy (video case 2). Final angiographic result (left anterior oblique 30). After orbital atherectomy, were dilated with a 2.5-mm balloon and then used IVUS to determine the stent length and distal reference diameter. We placed a 3.0 × 48 everolimus eluting stent in the mid RCA. We overlapped proximally with a 3.5 × 20 everolimus stent. After dilatation was performed with 3.25 NC and 3.5 NC balloons and a 4.0 NC in the proximal or ostial RCA.

12.11: Right coronary artery treated with orbital atherectomy (video case 2). Final angiographic result (right anterior oblique 30).

13 Treatment of In-Stent Restenosis

13.1: Treatment of drug-eluting stent in-stent restenosis with drug-coated balloon therapy.

13.2: Treatment of drug-eluting stent in-stent restenosis with drug-coated balloon therapy.

13.3: Treatment of drug-eluting stent in-stent restenosis with drug-coated balloon therapy.

13.4: Diffuse in-stent restenosis showing features of in-stent neoatherosclerosis by optical coherence tomography.

13.5: Diffuse in-stent restenosis showing features of in-stent neoatherosclerosis by optical coherence tomography.

13.6: Diffuse in-stent restenosis showing features of in-stent neoatherosclerosis by optical coherence tomography.

13.7: Diffuse in-stent restenosis showing features of in-stent neoatherosclerosis by optical coherence tomography.

13.8: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.9: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.10: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.11: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.12: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.13: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.



13.14: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.15: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.16: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.17: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.18: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.19: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.20: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.21: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

13.22: Angiographic classification of restenosis after bare-metal and drug-eluting stenting.

14 Management of Thrombotic Lesions

14.1: Saphenous vein graft occlusion. The site of occlusion is proximal to the previously placed stent.

14.2: Aspiration thrombectomy.

14.3: Improved but still poor flow after aspiration thrombectomy.

14.4: Rheolytic thrombectomy.

14.5: Successful reperfusion after rheolytic thrombectomy with the AngioJet Spiroflex device.

15 Fractional Flow Reserve and Nonhyperemic Pressure Ratios

15.1: Left main fractional flow reserve.

16 Intravascular Ultrasound Imaging

16.1: Strut malapposition.

16.2: Stent strut malapposition.

16.3: Use of intravascular imaging in locating an occluded ostium.

16.4: Guide catheter-induced dissection.

16.5: Intravascular ultrasound guidance of ostial chronic total occlusion percutaneous coronary intervention.

16.6: Intravascular ultrasound-guided reentry in chronic total occlusion superficial femoral artery percutaneous angioplasty.

18 Intervention for Lower Extremity Arterial Disease

18.2: Treatment of a chronic total occlusion of the right common iliac artery using retrograde access from the right common femoral artery and access from the left radial artery. Intravascular ultrasound was used to confirm the wire location in the artery before stenting.

18.3: Covered self-expanding stent to a large dissection in the left external iliac artery after treatment of a chronic total occlusion.

18.4: Intravascular lithotripsy and orbital atherectomy followed by drug-coated balloon treatment of a heavily calcified chronic total occlusion of the right common femoral artery lesion.

18.5: Laser atherectomy and orbital atherectomy of a heavily calcified popliteal artery occlusion.

18.6: Catheter-directed thrombolysis of an occluded popliteal artery stent.

20 Renal Artery Intervention: Catheter-Based Therapy for Renal Artery Stenosis

20.1: Baseline left renal stenosis.

20.2: After stenting of left renal stenosis.

21 Mesenteric Artery Intervention: Catheter-Based Therapy for Chronic Mesenteric Ischemia

21.1: Superior mesenteric artery ostial stenosis.

21.2: Superior mesenteric artery after stenting.

22 Renal Denervation

22.1: Femoral access has been obtained. A 6-Fr internal mammary catheter is advanced into the abdominal aorta over a 0.035-inch wire (e.g., Terumo, Somerset). The guide catheter is connected to a manifold or power injector and, while the wire is kept in place, and when the catheter tip is in the proximity of the renal arteries (typically at the L1–L2 transition), contrast is injected during cine-angiography to illustrate the renal arteries. Alternatively (not shown here), a pigtail catheter can be advanced over an 0.035-inch wire into the abdominal aorta with the tip located at the L1–L2 transition, and abdominal angiography can be performed.

22.2: The guide catheter is rotated with its tip oriented to the anticipated ostium of the right renal artery while the wire is left in the aorta. When the catheter tip is pointing toward the right renal artery ostium, the wire is slowly withdrawn to allow the catheter tip to “passively” engage the renal artery. This may minimize undue trauma to potential atherosclerotic plaque in the abdominal aorta during guide catheter manipulation.

22.3: The SPYRAL catheter is advanced over a 0.014-inch guidewire into the renal artery.

22.4: The guidewire is retracted partially, allowing the spiral portion of the SPYRAL catheter to assume its shape and the electrodes to establish contact with the renal artery wall.

22.5: Peregrine system catheter guide tube deployment.

22.6: Peregrine system catheter needle deployment.

22.7: The Peregrine system catheter (Ablative Solutions) with the needles deployed and right renal artery angiography to assure needle penetration into the adventitia and perirenal space.

22.8: Demonstration of microextravasation after Peregrine catheter needle and guide tube retraction.

23 Endovascular Management of Aortic and Thoracic Aneurysms

23.1: Step-by-step approach to percutaneous preclose for endovascular aneurysm repair.

23.2: Step-by-step deployments of endovascular aneurysm repair stent graft (Gore Excluder C3).

24 Carotid and Vertebral Intervention

24.1: Asymptomatic carotid stenosis treated with filter embolic protection and stent.

24.2: Symptomatic carotid stenosis treated with proximal flow arrest (Mo.Ma device) embolic protection and stent.

26 Interventional Management of Lower Extremity Deep Vein Thrombosis and Pulmonary Embolism

26.1: Standard deployment of a retrievable filter in the infrarenal inferior vena cava.



26.2: Standard filter retrieval using a gooseneck snare to collapse the filter into a sheath placed via the right internal jugular vein.

27 Management of Chronic Venous Insufficiency

27.1: Iliac vein compression by the iliac artery as seen with intravascular ultrasonography before treatment.

27.2: Iliac vein compression treated with a self-expanding stent as seen with intravascular ultrasonography.

28 Hemodialysis Access Intervention

28.1: Step 1: thrombectomy of thrombosed right forearm brachial-cephalic prosthetic graft in the outflow direction.

28.2: Step 1: thrombectomy of thrombosed right forearm brachial-cephalic prosthetic graft in the inflow direction.

28.3: Step 2: identification of the culprit stenosis identified at venous anastomosis after flow is achieved.

28.4: Step 2: balloon angioplasty of culprit stenosis.

28.5: Step 2: angioplasty result.

28.6: Step 3: Fogarty embolectomy of resistant thrombus at arterial anastomosis.

28.7: Step 4: central venous angiography.

29 Structural Heart Intervention

29.1: Aortogram identifying the coplanar view for Sapien XT valve deployment.

29.2: [To come]

29.3: [To come]

29.4: Aortogram identifying the view for CoreValve deployment.

29.5: Deployment of the CoreValve prosthesis.

29.6: Final position of the CoreValve prosthesis.

30 Transcatheter Mitral Valve Intervention

30.1: Fluoroscopy of a Brockenbrough needle crossing the interatrial septum with the pigtail in the ascending aorta.

30.2: Mullins sheath advanced into the left atrium from the right atrium over a wire after the transeptal puncture.

30.3: Three-dimensional transesophageal echocardiogram showing septal puncture (posterior).

30.4: Three-dimensional transesophageal echocardiogram showing septal puncture (anterior).

30.5: Severe mitral regurgitation by three-dimensional transesophageal echocardiography (before MitraClip).

30.6: Double-orifice mitral valve after transcatheter edge-to-edge repair with two MitraClips.

31 Transcatheter Tricuspid Valve Intervention

31.1: TriClip edge-to-edge repair for treatment of severe tricuspid regurgitation: before intervention.

31.2: TriClip edge-to-edge repair for treatment of tricuspid regurgitation: after insertion of two clips.

32 Hypertrophic Cardiomyopathy

32.1: Procedural technique for alcohol septal ablation.

33 Patent Foramen Ovale, Atrial Septal Defect, Left Atrial Appendage, and Ventricular Septal Defect Closure

33.1: Thrombus in transit through a patent foramen ovale, seen on transthoracic echocardiogram.

33.2: Intracardiac echocardiography guidance during transcatheter patent foramen ovale closure using a Helex device.

33.3: Intracardiac echocardiography guidance during transcatheter secundum atrial septal defect closure using the Amplatzer atrial septal Occluder device.

33.4: Fluoroscopic images during transcatheter secundum atrial septal defect closure using the Amplatzer atrial septal Occluder device.

33.5: Atrial septal defect with deficient aortic rim. A, Three-dimensional transesophageal echocardiogram. B, Two-dimensional transesophageal echocardiogram.

33.6: Watchman fix.

33.7: Peridevice leak with evidence of to-and-fro color Doppler signal at the edge of a Watchman device.

33.8: Watchman thrombus on computed tomography.

33.9: Amulet device.

33.10: Echocardiography guidance and fluoroscopy during transcatheter post-myocardial infarction ventricular septal defect closure.

34 Interventions for Advanced Heart Failure

34.1: Cine-angiography of a continuous flow left ventricular assist devices.

34.2: Cine-angiography of an Impella 5.0 LP device deployed via surgical cutdown of the right axillary artery.

34.3: Pressure volume loop derived from activation of an Impella 5.0 LP device in an acute, swine model of left ventricular injury.

34.4: Cine-angiography of an activated TandemHeart device reducing left ventricular volume and pressure as evidenced by stasis in the left ventricle and minimal opening of the mitral valve.

34.5: Pressure volume loop derived from activation of a TandemHeart device in an acute, swine model of left ventricular injury.

34.6: Pressure-volume loop derived from activation of venoarterial extracorporeal membrane oxygenation in an acute, swine model of left ventricular injury.

35 Endomyocardial Biopsy

35.1: A, Native right ventricular (RV) septal biopsy using fluoroscopy in the posteroanterior (PA) projection. B, Native RV septal biopsy using fluoroscopy in the left anterior oblique projection. C, Native RV septal biopsy done with echocardiographic guidance. D, Native RV septal biopsy in PA projection, with opening and closing of the biptome.

35.2: Native right ventricular (RV) septal biopsy to rule out amyloid on echocardiography, but the biptome is facing the RV free wall.

36 Pericardiocentesis and Pericardial Intervention

36.1: Needle access for pericardiocentesis with confirmatory contrast injection.

36.2: Percutaneous pericardial biopsy using a standard BiPal 55-cm biopsy forceps.

36.3: Percutaneous pericardial biopsy using a standard BiPal 55-cm biopsy forceps.

36.4: Needle access for percutaneous transpericardial left atrial appendage occlusion using the LARIAT device.

36.5: Baseline left atriography in a right anterior oblique projection with the 12-Fr LARIAT delivery sheath advanced into the pericardial space.



36.6: Baseline left atriography in a left anterior oblique projection with the 12-Fr LARIAT delivery sheath advanced into the pericardial space.

36.7: Successful alignment and connection of both magnetic 0.025- and 0.035-inch guidewires, respectively. Advancement of the snare device over the left atrial appendage apex toward the base.

36.8: Completion Left atrial angiography confirming occlusion of the left atrial appendage (LAA) by the device with only minor residual flow into the base of the LAA.

37 Adult Congenital Heart Disease: Cardiovascular Interventions for Pulmonary Arterial Hypertension, Anomalous Vascular Connections, Aortic Coarctation, and Pulmonary Valve Replacement

37.1: Anteroposterior projection of selective coronary angiography of the left coronary artery system demonstrating a distal left coronary artery–right ventricle fistula.

37.2: Anteroposterior projection demonstrating a left lung arteriovenous malformations in a patient with complex heterotaxy syndrome and single-ventricle physiology.

37.3: Inferior vena cava angiogram in a child with heterotaxy syndrome and single-ventricle physiology.

37.4: Lateral cineangiogram of balloon pulmonary valvuloplasty.

37.5: Lateral cineangiogram of a hand injection done to confirm appropriate stent location before deployment.

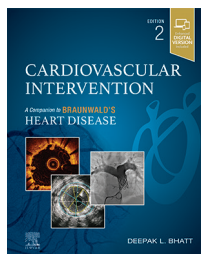
37.6: Anteroposterior cineangiogram, with the catheter in the left ventricle (LV), in a neonate with critical aortic stenosis, severe mitral regurgitation, and severe LV dysfunction.

37.7: Anterior-posterior cineangiogram of balloon aortic valvuloplasty using an antegrade approach in the same patient.

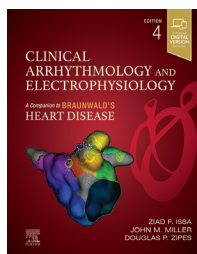
37.8: Anterior-posterior cineangiogram, with the catheter in the left ventricle (LV), following balloon aortic valvuloplasty.



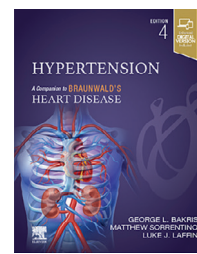
Braunwald's Heart Disease Family of Books



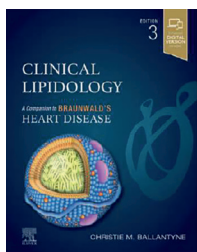
BHATT
Cardiovascular Intervention



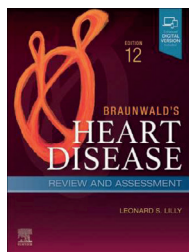
ISSA, MILLER, ZIPES
*Clinical Arrhythmology and
Electrophysiology*



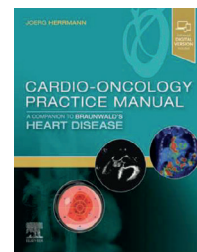
BAKRIS, SORRENTINO, AND LAFFIN
Hypertension



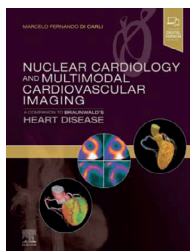
BALLANTYNE
Clinical Lipidology



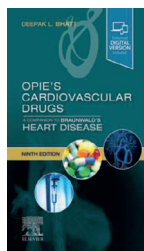
LILLY
*Braunwald's Heart Disease
Review and Assessment*



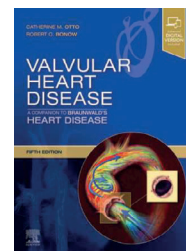
HERRMANN
*Cardio-Oncology Practice
Manual*



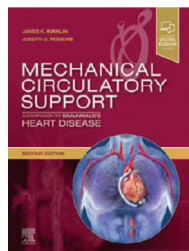
DI CARLI
*Nuclear Cardiology and Multi-
modal Cardiovascular Imaging*



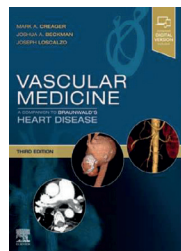
BHATT
Opie's Cardiovascular Drugs



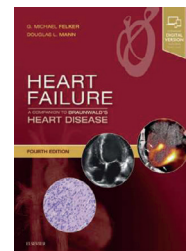
OTTO AND BONOW
Valvular Heart Disease



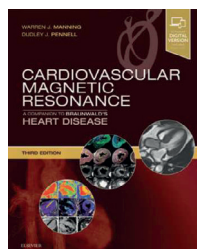
KIRKLIN AND ROGERS
Mechanical Circulatory Support



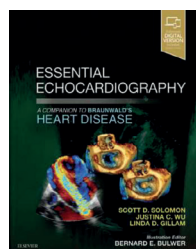
CREAGER
Vascular Medicine



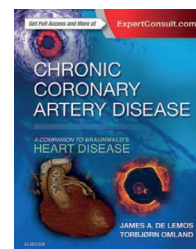
FELKER AND MANN
Heart Failure



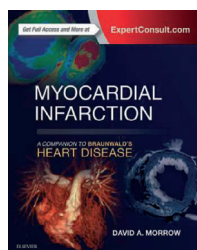
MANNING AND PENNELL
Cardiovascular Magnetic Resonance



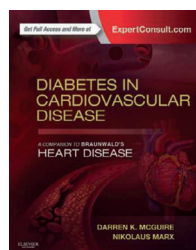
SOLOMON, WU, AND GILLAM
Essential Echocardiography



DE LEMOS AND OMLAND
Chronic Coronary Artery Disease



MORROW
Myocardial Infarction



MCGUIRE AND MARX
Diabetes in Cardiovascular Disease



CARDIOVASCULAR INTERVENTION

A Companion to **BRAUNWALD'S**
HEART DISEASE



1 The Birth Of Interventional Cardiology

DAVID O. WILLIAMS

THE INNOVATOR OF ANGIOPLASTY, 1

THE FIRST PERIPHERAL ARTERIAL ANGIOPLASTY, 2

THE DEVELOPMENT OF CORONARY ANGIOPLASTY, 2

CORONARY ANGIOPLASTY THEN AND NOW, 3

ACUTE ANGIOPLASTY FAILURE, 3

MECHANISM OF BALLOON ANGIOPLASTY, 4

DISSEMINATION OF CORONARY ANGIOPLASTY, 4

ANDREAS GRÜNTZIG, THE MAN, 5

DEVELOPMENT OF INTERVENTIONAL CARDIOLOGY AND MINIMALLY INVASIVE SURGERY, 5

THE INNOVATOR OF ANGIOPLASTY

There are few who are acknowledged as true pioneers in medicine, but Andreas Grüntzig was surely one (Figure 1.1). He quite simply not only coined the term *interventional cardiology*, but he *was* interventional cardiology. For many evenings, Grüntzig, his wife Michaela, and Walter and Maria Schlumpf sat at the Grüntzigs' kitchen table fabricating balloon catheters. These catheters were the prototypes that enabled Grüntzig to eventually effectively treat patients with peripheral and coronary artery disease without surgery. In September 1977, Grüntzig performed the first successful coronary angioplasty, which he did on Dolf Bachmann. This event initiated a cascade of innovations that have greatly changed the approaches and techniques for the treatment of patients with coronary disease as well as for others who have required traditional surgical procedures. This chapter discusses the origin of angioplasty and the story of its inventor.

Andreas Roland Grüntzig was born in Dresden, Germany, June 25, 1939. He was the second child of Charlotta and Wilmar Grüntzig. Andreas was a child of World War II. He had one brother, Johannes, who was older. The boys quickly lost their father, a secondary-school science teacher, who was conscripted as a weatherman for the Luftwaffe.¹

Based on concerns for her family's safety, Charlotta and her two boys moved from one home to another in Germany, then to South America, and then back again. After World War II, the fatherless family settled in Leipzig, then a part of East Germany. Day after day, Charlotta and her two boys went to the local train station, eyeing the German troops returning from the Eastern front. They were waiting for Wilmar, who never arrived.

Although both boys performed well in school, East German rules of the day demanded they become laborers because their father had been educated. This concept did not sit well with either boy. West Germany was potentially

accessible to Johannes and Andreas. As teenagers, they occasionally snuck across the border at night for brief social excursions. Finally, to pursue more desirable lives, Andreas, then age 17, and Johannes moved permanently to West Germany. They left their mother behind. How these boys were formally educated in this new country is unclear, but eventually they attended medical school at the University of Heidelberg.

Toward the end of this medical school curriculum, Andreas Grüntzig began a series of clinical rotations. These took him to several European venues. At 28 years of age, he attended the London School of Economics. There he studied epidemiology and statistical methods. This experience was critical and provided the basis for his approach to evaluating the effectiveness and safety of coronary angioplasty.

At 30 years of age, Grüntzig was accepted to the internal medicine training program at the University of Zurich (Figure 1.2). His educational plans were disrupted when the program director died unexpectedly. Fortunately for Grüntzig, who had just moved to Zurich, Alfred Bollinger offered him a training position in "angiology." Angiology was and remains an established medical discipline of European medicine. Grüntzig accepted. This opportunity exposed him to patients with peripheral artery disease, the substrate for his concept of balloon angioplasty.

While in training, Grüntzig heard a lecture by Eberhard Zeitler of the Aggertal Clinic about the "Dotter procedure" named after US physician Charles Dotter. Dotter lived in Oregon and as a vascular radiologist had developed a technique for dilating atherosclerotic stenoses of peripheral arteries. He called the technique "transluminal dilatation," a term Grüntzig later borrowed when initially labeling coronary angioplasty.

The Dotter procedure involved crossing a stenotic arterial segment with a guidewire and then sequentially advancing progressively larger, tapered end-hole catheters



FIGURE 1.1 Andreas Grüntzig during a coronary angioplasty. (Courtesy of Dr. Gary S. Roubin.)

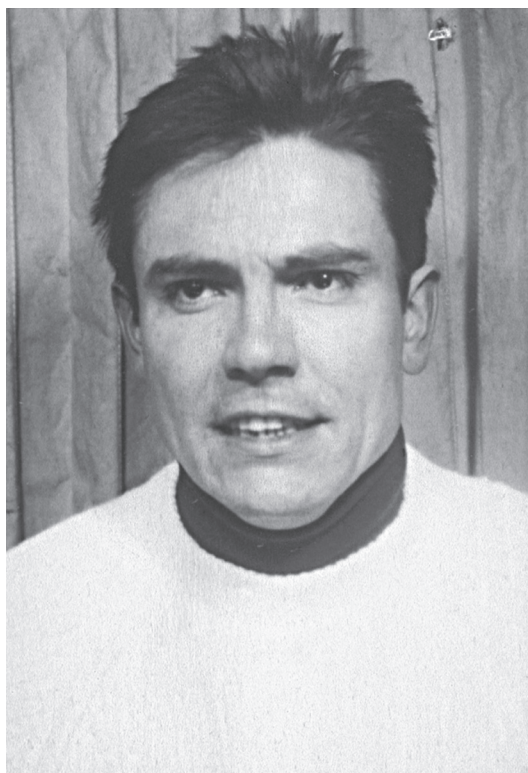


FIGURE 1.2 Photograph Andreas Grüntzig submitted with his application for training in internal medicine at University Hospital, Zurich. (Courtesy of Ernst Schneider, MD.)

across the narrowed segment. The actual relief in stenosis severity was quite modest, yet in many instances clinical improvement was substantial. Although this procedure was innovated in the United States, it was not well accepted by American physicians. Zeitler, however, had adopted the technique with enthusiasm. In 1971, he was performing Dotter procedures on a regular basis. Grüntzig met Zeitler, observed him, and eventually assisted him.

After returning to Zurich, Grüntzig began to perform Dotter's procedure, with mixed success. Resident vascular surgeons focused on complications of the procedure such as groin hematomas. Moreover, improvement of Grüntzig's skill was hampered by limited access to patients. In the back of his mind, however, was the thought of a different

approach, namely a balloon-tipped catheter that could dilate stenotic arteries.

Grüntzig's laboratory for innovation was the kitchen of his and Michaela's two-bedroom flat. The team included Andreas; Michaela; Maria Schumpf, Andreas' assistant; and her husband, Walter, an engineer by training. Identifying and obtaining materials that could serve appropriately for the catheter shafts and balloons were challenges. Grüntzig eventually selected polyvinyl chloride (PVC) as the balloon material for his catheters. This was a unique substance, particularly strong, and could be easily shaped. In fact, PVC was being used for making disposable bottles of Coca-Cola. Progress was slow, but over a period of 2 years and hours of cutting and gluing, a balloon catheter was fabricated that repeatedly yielded predictable performance.

The initial catheter was a single-lumen system. After being advanced over a guidewire and in proper position, the guidewire was removed, and a tip-occluding wire was placed in the catheter. Fluid injected into the catheter lumen then filled the balloon by means of side holes or skives in the catheter shaft.

THE FIRST PERIPHERAL ARTERIAL ANGIOPLASTY

It was on February 12, 1974, that Grüntzig used this catheter to dilate the iliac artery of a 67-year-old man in Zurich. The procedure was successful by all parameters: angiographic and hemodynamic assessments as well as the patient's clinical response.

Although the risks were undoubtedly greater and the technical demands more difficult, coronary disease was always a goal for Grüntzig. Different but significant clinical challenges were unique to the coronary circulation. What would be the consequences of transient coronary occlusion? Would there be irreversible myocardial infarction? Would patients experience ventricular fibrillation? Thoughts such as these stimulated him to develop a two-lumen balloon catheter. One lumen would maintain coronary perfusion; the other lumen would be used for the balloon inflation. Navigation of the catheter would be difficult but aided with a short, fixed wire at its tip to assist in entering the correct coronary artery and crossing the stenotic segment.

The logical testing site for the first double-lumen new catheter would be a peripheral artery. In January 1975, Grüntzig used his balloon catheter to dilate an iliac artery stenosis. The procedure was successful! Over the next 2 years, he performed more than 200 peripheral arterial balloon angioplasties.

THE DEVELOPMENT OF CORONARY ANGIOPLASTY

Creating a "model" to test a coronary angioplasty balloon catheter was the next logical step prior to attempting coronary angioplasty in a patient. To accomplish this, Grüntzig created coronary stenoses in anesthetized open-chest dogs by placing sutures around the coronary arteries. Then with the aid of fluoroscopic guidance, he advanced



his balloon-tipped catheters into the constricted coronary and dilated the ligated segment. Gruntzig presented this work at the Miami meeting of the American Heart Association in November 1976. Although his presentation was well attended, the prevailing response was skeptical.

Little is known about the very first attempted coronary angioplasty in humans. The patient was a 66-year-old man with cardiogenic shock who had been rejected for cardiac surgery. In an effort to rescue the patient, Andreas attempted coronary angioplasty in Zurich in early 1977. Access was a problem. After an unsuccessful femoral arterial approach, he eventually obtained access from the left brachial artery. An unwieldy, 9-Fr Teflon guide catheter was inserted. Gruntzig could not engage the catheter into the left coronary ostium, and the procedure was aborted.

Gruntzig's next steps were more cautious and modest. With the aid of Richard Myler of San Francisco, Gruntzig pursued a different approach. They evaluated his balloon catheters in the operating room (OR) during coronary bypass operations. After the coronary arteriotomy was made, catheters were advanced to the lesion, and the balloon was inflated. After a handful of cases, they concluded that Andreas's catheters could dilate coronary lesions.

In September 1977, Andreas met Dolf Bachmann. Like Andreas, Bachmann was 38 years old. Unlike Andreas, he had severe angina, taking up to 15 sublingual nitroglycerine tablets a day. He was adamantly opposed to coronary bypass surgery. After consultation with Gruntzig, he agreed to be the first patient to have coronary angioplasty. Importantly, he also agreed to coronary bypass surgery if angioplasty failed.

With a surgical OR on standby, Bachmann's procedure was performed on September 16. Andreas advanced a 3.0-mm short wire-tipped balloon catheter across a left anterior descending lesion and inflated the balloon. A second lumen in the balloon catheter, originally designed to deliver blood flow during balloon inflation, was used to measure coronary arterial pressure proximal and distal to the stenosis. When the balloon catheter crossed the stenosis, the balloon catheter tip pressure fell. After the initial inflation, the distal pressure rose. According to protocol, the balloon catheter was withdrawn proximal to the lesion, which had improved substantially by angiography. The catheter was then readvanced across the lesion, and a second inflation was performed. Angiography after withdrawal of the balloon catheter revealed no significant lesion. The case was a remarkable success. Gruntzig labeled this new procedure percutaneous transluminal coronary angioplasty (PTCA).

The following day, Bachmann was completely asymptomatic and so overjoyed that he called a newspaper journalist. Gruntzig, ever a scholar and aware of the adverse potential consequences that might arise from a tabloid report, convinced Bachmann to hold off. The official accounting of this first successful case of PTCA was subsequently published in the February 4, 1978 issue of *Lancet*.

CORONARY ANGIOPLASTY THEN AND NOW

Several aspects of that first case and subsequent ones for the initial years thereafter are noteworthy when compared

with coronary intervention performed today. Access to coronary arteries was difficult. Guide catheters were large, 9 Fr, and mostly unresponsive to manipulation and rotation.

There were no over-the-wire balloon catheters. Balloon catheters had only a short, fixed wire at the tip, and torque was poorly transmitted to the distal end of the catheter. Also, balloon catheters were in short supply. It took an entire day to manufacture one balloon catheter, and there was only one individual, Hans Gleichner of Schneider Corporation, who could fabricate them. As a consequence, balloon catheters were reused among patients. Between cases, balloon catheters soaked in a bowl containing Cidex, an antiseptic solution. During a case, catheters were removed from the bowl, wiped with a saline sponge, and inserted into the patient.

Balloon catheters were routinely withdrawn proximal to the dilated lesion after balloon inflation. There had been fear that leaving catheters distal to lesions would impair coronary perfusion. Techniques were crude, and recrossing initially dilated lesions often resulted in exacerbation of dissection and even abrupt coronary occlusion.

There were no valves on the large 9-Fr sheaths, and serious groin bleeds and the need for blood transfusions were common. Venous sheaths were required because a temporary pacemaker was routinely placed into the right ventricle for every patient. No one had any experience with the incidence of cardiac rhythm disturbance as a consequence of brief coronary occlusion, so precautions were initiated.

ACUTE ANGIOPLASTY FAILURE

There was always the concern that angioplasty could fail, and the operator would have to deal with the consequences of not only lack of success but also of acute coronary occlusion. With the crude initial tools then available, very early rates of abrupt closure approximated 20% to 30%. A large proportion of patients experienced acute myocardial infarction as a consequence of unsuccessful angioplasty. Consequently, a very close, supportive relationship with cardiac surgery was essential. In the early years, each patient had a formal consultation by a cardiac surgeon before PTCA, and the procedure was not started unless an OR was free and an entire surgical team was available.

To minimize abrupt closure, full heparinization was maintained during procedures. If the angioplasty was successful, arterial and venous femoral sheaths were left in place. Patients recovered in the coronary care unit, a site where vigilant observation and nursing care were available. These early cases were difficult for both patients and physicians. Aside from bleeding, procedures took considerable time. With all that was involved and with a lack of training and experience, performing just one case a day could be exhausting.

Several other important lessons became evident early in the course of angioplasty. One related to the role of PTCA for patients with significant stenosis of their left main coronary artery. Given the difficulties in manipulating angioplasty catheters deep into a coronary artery, left main angioplasty appeared simple. Early in his PTCA

experience, Grüntzig was initially successful when he first treated a patient with left main disease. The patient left the hospital in improved condition, and follow-up stress testing showed relief of ischemia. But then, Andreas received news that the patient had died suddenly at home. The timing of the death suggested that restenosis rather than acute abrupt closure was the more likely explanation. This experience led to the realization that restenosis, which is common after percutaneous coronary intervention (PCI), located in the left main coronary artery could result in ischemia of sufficient magnitude to cause death.

MECHANISM OF BALLOON ANGIOPLASTY

How did balloon angioplasty work? For Grüntzig, the explanation was simple. He likened the explanation to “foot-prints in the snow.” In fact, when he lectured about his procedure, he routinely displayed a slide showing depressions in deep snow from human footprints. Such an explanation made sense, and to some degree, a component of plaque compression likely did result from balloon inflation. Subsequently, pathologic studies indicated that atherosclerotic plaques were actually torn as the diameter of the artery was enlarged circumferentially. Plaque fracturing was accompanied by an increase in the circumference of the external elastic membrane. Pathologic studies from acute and late deaths demonstrated the response to this local injury was neoproliferation of tissue within the dilated arterial wall.² Almost in an effort to “repair” damage caused by balloon inflation, media-derived cells proliferated in the crevices of the dilated plaque. Ideally, this proliferation would fill these new crevices and create a smooth and enlarged arterial lumen. However, it became clear that neoproliferation could be more exuberant and extend into the arterial lumen. It could then accumulate to the point where arterial narrowing could develop and the patient could become ischemic again. This latter process was termed *restenosis*.

DISSEMINATION OF CORONARY ANGIOPLASTY

Andreas Grüntzig took another bold step in the fall of 1978 when he organized a “demonstration course” held at the University Hospital in Zurich to allow others to learn this new form of coronary revascularization. Such an activity was unheard of in cardiology. Certainly, demonstrations of surgical procedures had been performed previously, but never had anyone publicly demonstrated a procedure performed in a cardiac catheterization laboratory. Furthermore, PTCA was in its infancy, and serious consequences such as abrupt coronary occlusion, myocardial infarction, and even death were possible outcomes.

Approximately 35 physicians attended this initial course, including the author. We sat in a small, classic amphitheater and observed Andreas perform two PTCA cases a day for 5 days. Each case was televised to the lecture hall from the catheterization laboratory. Of the 10 procedures, approximately half were successful. Of the unsuccessful ones, a substantial proportion of patients had abrupt

coronary occlusion and electrocardiographic evidence of acute ST-segment elevation. Each of the unsuccessfully treated patients underwent immediate coronary bypass surgery. There were no deaths.

Reactions of attendees were mixed. Some senior cardiologists were appalled and believed the procedure was improper and no match for coronary bypass surgery. Others were impressed by the successfully treated patients and sensed the potential implications of this new procedure.

Notable were the thoroughness, intellectual honesty, and frankness of Grüntzig. He presented the history and clinical presentation of each patient, discussed the potential benefits and risks of both PTCA and coronary artery bypass grafting (CABG), and narrated as he performed each procedure. His demeanor, calmness, and obvious skill were remarkable. After a case was completed, he returned to the amphitheater and reviewed each step of the prior procedure. The procedures we witnessed were truly astonishing and only exceeded by the skill and daring of the man who performed them.

After this initial demonstration, angioplasty began to spread. By the end of 1978, Richard Myler, Simon Stertzer, Lamberto Bentivoglio, David Williams, and Peter Block performed PCI in the United States. Other physicians brought patients to US angioplasty sites and observed this new therapeutic approach.

Grüntzig published his initial 50 case experiences in the *New England Journal of Medicine* in July 1979.³ In that report, coronary lesion dilation was achieved in 32 (64%) patients, and 29 (58%) improved clinically. Of interest, Grüntzig estimated that only 10% to 15% of patients with coronary disease had lesions suitable for PTCA.

Michael Mock, then at the National Heart, Lung, and Blood Institute, initiated a National Institutes of Health-funded registry to characterize and describe the patients treated by PTCA and their outcomes. Katherine Detry and Sheryl Kelsey headed the data coordinating center at the University of Pittsburgh. This registry captured consecutive cases performed in Zurich and the United States and became an important mechanism for reporting valuable information about this new procedure.⁴

Grüntzig held additional Zurich demonstration courses in the spring and fall of 1979. There were several differences between these and the first demonstration. First, within a short interval, PTCA had become acknowledged as a legitimate option for coronary revascularization. Grüntzig's openness and objectiveness had added credibility to his achievements and the procedure. Physicians who attend accepted the procedure and thirsted to learn the technique. Second, the news of PTCA had spread such that the number of physicians who attended was now measured in the hundreds. Third, the worldwide experience of PTCA elsewhere was still limited. During this course, Grüntzig queried each operator who had performed PTCA and the numbers of cases each had performed. He wrote and totaled their results on a blackboard. This was the worldwide experience. Fourth, some physicians saw PTCA as an opportunity for personal advancement. At times, these individuals jockeyed for stature and attempted to establish themselves as legitimate authorities. Certainly, the tone of this meeting was quite different from that of the first.



ANDREAS GRÜNTZIG, THE MAN

In orchestrating these courses, Grüntzig always included some form of social activity during evenings. These included a boat trip on Lake Zurich, a train to Emmental (the home of Swiss cheese), and a trek to the top of a nearby mountain. Grüntzig was just as comfortable and skillful in these settings as he was in the catheterization laboratory. Many close personal relationships formed among attendees that lasted for decades.

As PTCA grew, so did the reputation of the man who developed the procedure. Grüntzig became a target for recruitment, particularly for medical institutions in the United States. Eventually, Grüntzig joined the faculty of Emory University, which provided the appropriate backdrop to further the growth of PTCA, which he renamed percutaneous coronary intervention. Andreas's wife Michaela joined him there but found the American way of life difficult for her socially and professionally. After a short time, she returned to Zurich to reside in the same apartment where she and Andreas developed the very first angioplasty catheters.

With the aid of Spencer King and John Douglas, Grüntzig grew the angioplasty program at Emory. The theme of bi-annual training courses continued with multiple, increasingly complex procedures demonstrated daily. There, Grüntzig met Margret Anne Thornton, an Emory medical student. He was so charmed by this Georgia native that he divorced Michaela and married Margret Anne. Within a short time, they purchased an estate in tony Buckhead and a second home in Sea Island, Georgia.

Always a traveler of the fast lane, Grüntzig bought a new car, a Porsche 911. This was followed by a single-engine plane, which was perfect for access to their second home in Sea Island, Georgia. Seeking even greater goals, Grüntzig then purchased a twin-engine Beechcraft Baron. This plane, although more challenging to fly, was now affordable for Grüntzig and in fitting with his new stature.

On an overcast Sunday, October 27, 1985, Andreas, Margret Anne, and their two dogs, Gin and Tonic, departed Sea Island for Atlanta. Cloud cover was thick and low. Brief transcripts of recordings from Grüntzig to traffic control state that while in the air, he had difficulty using the autopilot system of the plane. Two hunters in a Georgia forest recalled seeing a plane descend from the overcast sky and fly straight into the earth. There was little at the crash site to identify who or what had been in the Grüntzig plane. A funeral service and burial for Andreas and Margret Anne was held in Macon, Georgia, Margret Anne's home. Ironically, three other pioneers of vascular medicine died that year: Melvin Judkins, Mason Sones, and Charles Dotter.

DEVELOPMENT OF INTERVENTIONAL CARDIOLOGY AND MINIMALLY INVASIVE SURGERY

The pioneering work of Grüntzig was followed by a series of innovations that incrementally improved clinical outcomes and advanced the field of interventional cardiology. Many engineers, cardiologists, and entrepreneurs attempted to

identify devices that would replace or supplement the balloon catheter. Metallic stents were the first significant advancement.⁵⁻⁸ Stents addressed two important shortcomings of balloon angioplasty, abrupt closure and late lesion recurrence.

Balloon angioplasty caused localized dissection of the arterial wall. If this dissection was too extensive, it caused an intimal flap or created a hematoma within the media, each of which could exacerbate rather than relieve coronary narrowing. Stents provided a rigid scaffold that compressed the arterial wall and minimized the likelihood of abrupt closure. Stents have been so effective that sustained abrupt closure is very rare, such that PCI can now be performed safely in the absence of on-site CABG.⁹

A second shortcoming of balloon angioplasty was lesion recurrence. Angiographic assessment of sites of balloon angioplasty indicated a recurrence rate, defined as more than a 50% residual narrowing, of approximately 30% to 40%.¹⁰ Multiple pharmacologic cocktails were proposed and tested to reduce the incidence of restenosis; each failed. New devices for the removal of plaque were intensely investigated.^{11,12} None matched the results of a coronary stent. Although stents prevented the negative remodeling that followed balloon angioplasty, neointimal hyperplasia was more pronounced. Furthermore, if in-stent restenosis did develop, repeat balloon angioplasty was of limited benefit because lesion recurrence was common. Use of local radiation as a mechanism to prevent neoproliferation was quite successful in reducing rates of in-stent restenosis.^{13,14}

The definitive approach to treat intimal hyperplasia locally was to add potent antiproliferative agents to stents, thus making stents local drug delivery systems.¹⁵ This final combination coupled with improving stent materials and design and adding low-profile delivery catheters resulted in very low rates of short-term complications. During later follow-up, however, recurrent symptoms and events can develop and are related to the extent of underlying coronary disease and disease progression.¹⁶

Coronary balloon angioplasty established the concept of minimally invasive surgery. Angioplasty was the very first procedure to accomplish what could be achieved only by a coronary artery bypass operation. Grüntzig's achievements resulted in efforts to identify alternative, less invasive approaches to all types of surgical procedures. Laparoscopic surgery, now the standard of care, is just one example. Transcatheter aortic valve replacement is another example, one that is revolutionizing the minimally invasive approach to the treatment of patients with valvular heart disease.

Also of interest is that as innovators have attempted to create more advanced therapeutic approaches to coronary disease, balloon angioplasty remains the backbone. Drills, lasers, lithotripsy, and suction and cutting devices have been attached to catheters and evaluated as tools to remove atheromatous arterial obstruction and enhance coronary blood flow. Except for unusual circumstances, such as a heavily calcified stenosis, none has proved superior to balloon angioplasty and stenting.¹⁷

Andreas Grüntzig was an exceptional human being. His courage, innovation, determination, and just plain hard work provided the substance for his enormous



contribution. We will never know what other accomplishments he might have achieved had he not died prematurely and so tragically.

ACKNOWLEDGMENT

The author acknowledges the assistance of Carol A. Williams in the preparation of this manuscript.

REFERENCES

1. Monagan D, Williams DO. *Journey Into the Heart*. Gotham; 2007.
2. Ferns GAA, Avades TY. The mechanisms of coronary restenosis: insights from experimental models. *Int J Exp Pathol*. 2000;81:63-68.
3. Grüntzig AR, Senning A, Siegenthaler WE. Nonoperative dilation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med*. 1979;301:61-68.
4. Venkitachalam L, Kip KE, Selzer F, et al. Twenty-year evolution of percutaneous coronary intervention and its impact on clinical outcomes: a report from the NHLBI-sponsored, Multicenter Percutaneous Transluminal Coronary Angioplasty and 1997-2006 Dynamic Registries. *Circ Cardiovasc Interv*. 2009;2:6-13.
5. Schatz RA, Palmaz JC, Tio FO, et al. Balloon-expandable intracoronary stents in the adult dog. *Circulation*. 1987;76:450-457.
6. Sigwart U, Puel J, Mirkovitch V, et al. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med*. 1987;316:701-706.
7. Roubin GS, Cannon AD, Agrawal SK, et al. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. *Circulation*. 1992;85:916-927.
8. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med*. 1994;331:496-501.
9. Aversano T, Lemmon CC, Liu L, et al. Outcomes of PCI at hospitals with and without on-site cardiac surgery. *N Engl J Med*. 2012;366:1792-1802.
10. Holmes DR, Vlietstra RE, Smith HC, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the National Heart, Lung and Blood Institute. *Am J Cardiol*. 1984;53(12):77C-81C.
11. Baim DS, Cutlip DE, Sharma SK, et al. Final results of the balloon vs. optimal atherectomy trial (BOAT). *Circulation*. 1998;97:322-331.
12. Reifart N, Vandormael M, Krajcar M, et al. Randomized comparison of angioplasty of coronary lesions at a single center: excimer laser, rotational atherectomy and balloon angioplasty comparison (ERBAC) study. *Circulation*. 1997;96:91-98.
13. Leon MB, Tierstein PS, Moses JW, et al. Localized intracoronary gamma-radiation to inhibit the recurrence of restenosis after stenting. *N Engl J Med*. 2001;344:250-256.
14. Popma JJ, Suntharalingam M, Lansky A, et al. Randomized trial of 90SR/90Y beta-radiation versus placebo control for treatment of in-stent restenosis. *Circulation*. 2002;106:1090-1096.
15. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315-1323.
16. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main disease: 5-year follow-up of the randomized, clinical SYNTAX trial. *Lancet*. 2013;381:629-638.
17. Dill T, Dietz U, Hamm C, et al. A randomized comparison of balloon angioplasty versus rotational atherectomy in complex coronary lesions (COBRA study). *Eur Heart J*. 2000;21:1759-1766.



2 Guidelines And Appropriateness Criteria For Interventional Cardiology

DAVID P. FAXON

INTRODUCTION, 7

PRACTICE GUIDELINES, 7

Guideline Development, 7

Guidelines for Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction, 8

Guidelines for Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction, 11

Guidelines for Stable Ischemic Heart Disease, 12

APPROPRIATENESS CRITERIA, 17

Development Process, 17

Summary of Recommendations for Coronary Revascularization, 18

OTHER METHODS TO IMPROVE QUALITY, 18

Performance Measures, 18

Public Reporting, 19

PUTTING GUIDELINES INTO PRACTICE, 20

CONCLUSIONS, 21

INTRODUCTION

Quality of care has been a major focus of medical care since the Institute of Medicine (IOM) focused attention on the unacceptable degree of variability in care and concerns about patient safety and effectiveness. In its classic monograph *Crossing the Quality Chasm*, the IOM identified six aims to improve the quality of health care in the United States.¹ It stressed that health care needs to provide safe, effective, patient-centric, timely, efficient, and equitable care. Efforts to achieve these goals have resulted in the growth and widespread use of a number of tools to improve care, including practice guidelines, appropriateness criteria, performance measures, and methods to put guidelines in practice. Of these tools, practice guidelines have provided the foundation for the other quality efforts. Cardiology has been at the forefront of this process because of a large number of clinical studies and randomized trials upon which to base the guideline recommendations.

Califf² has described the “cycle of quality” to emphasize the continuous evolution of quality of care. As shown in [Figure 2.1](#), discoveries of new or improved diagnostic tools and optimal treatments are suggested by basic and translational science. Initial observational clinical trials lead to more definitive randomized controlled trials. The evidence derived from these studies forms the basis for consensus-driven guideline recommendations. Guidelines provide the foundation for the patient-specific recommendations of appropriateness criteria in which a number of key variables are integrated to best determine optimal use of procedures. Guidelines are also the basis for performance measures in which clearly defined and validated variables can be used to monitor the degree of quality and to reduce practice variability. New discoveries provide new directions or challenge prior practice and stimulate new clinical trials and the cycle repeats itself.

The explosion of guidelines over the past 20 years has been remarkable. Since 1995, the National Guideline Clearinghouse has identified 2352 practice guidelines, and of

these, 491 are in the cardiovascular area (www.guideline.gov). The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have published more than 100 guidelines since 2005, and the European Society of Cardiology (ESC) has also been active in publishing similar guidelines. The ACCF and AHA have been leaders in publishing appropriateness criteria for cardiovascular tests and procedures. Other organizations, such as the American Medical Association, in collaboration with the ACCF and AHA, have jointly published performance measures. In the cardiovascular field, the ACCF/AHA and ESC guidelines are the most respected and quoted documents.

PRACTICE GUIDELINES

Guideline Development

The ACCF and AHA have adopted a strict and rigorous process for guideline development.^{3,4} The joint guideline committee identifies topics of interest and selects a writing committee composed of recognized experts in the field, seasoned clinicians, generalists, and other health care providers from associated disciplines, including nurses and pharmacists. Recent recommendations are to also include a patient advocate. The evidence from clinical registries and trials is collated, rigorously reviewed, and analyzed to assist the committee in formulating its recommendations. These recommendations are categorized into four classes: Class I is defined as procedures or treatment that *should* be performed or administered, Class II indications are those in which it is *reasonable* to do the procedure or treatment (IIa) or when it *may be considered* (IIb), and Class III is defined as one that is anticipated to have *no benefit* or the procedure or treatment would cause *harm*. The level of evidence (LOE) for each recommendation is an important component of the process. Level A is used when the recommendation is supported by either multiple randomized trials or a meta-analysis, Level B-R is used

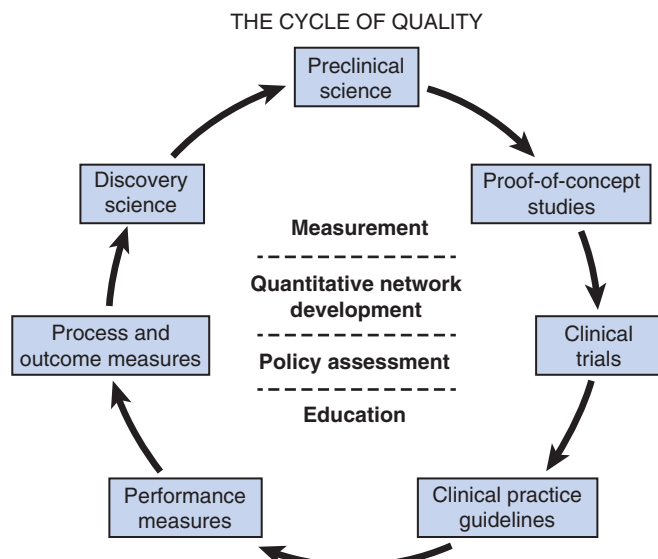


FIGURE 2.1 The cycle of quality. (Califf RM. The benefits of moving quality to a national level. *Am Heart J.* 2008;156:1019-1022.)

when the recommendation is supported by either a 1 or more randomized trials or meta-analysis or B-NR 1 or more nonrandomized studies or registries or meta-analysis, and Level C-LD is used when the recommendation is supported by studies with limitations of design or execution or meta-analysis of such studies or physiologic or mechanistic studies. Level C-EO is supported by consensus of expert opinion. The final guidelines document is peer reviewed by external experts and revised before the final document is approved by the participating organizations. The process is lengthy, which limits the ability to quickly revise the guidelines as new information from clinical trials alters practice. Efforts to improve the process and increase the speed and rigor of guideline development have been described.⁵ Although clinical trial data are critical to the formulation of guidelines, the lack of trials in many areas of practice unfortunately has resulted in Level C evidence (expert opinion), responsible for 48% of all guideline recommendations.⁶

For the purposes of this chapter, only current ACCF/AHA guidelines are reviewed, and only key recommendations that are directly pertinent to interventional cardiology practice are discussed. Please refer to the original documents for a more detailed discussion of the guidelines and the evidence supporting the recommendations. The 2021 ACC/AHA/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines for coronary artery revascularization provides the most current recommendations.⁷ They have built upon the 2018 ESC/European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularization.⁸ Both documents recommend the use of a heart team for decision making in patients in whom the optimal treatment strategy is unclear (Class I, B-NR).

Guidelines for Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction

The 2021 ACC AHA coronary revascularization guidelines and the 2018 ESC/EACTS guidelines on myocardial revascularization and the 2013 ACCAHA ST-segment elevation

myocardial infarction (STEMI) guidelines provide an in-depth discussion of the recommendations and the evidence supporting them.⁷⁻⁹

The guidelines recommend that the initial management of patients with an acute STEMI is the rapid reperfusion of the infarct artery. A reduction in the duration of the coronary occlusion results in reductions in infarct size and mortality rate. Of the two reperfusion strategies, fibrinolysis or angioplasty, percutaneous coronary intervention (PCI) is the preferred strategy when it can be performed expeditiously (Class 1A). The guidelines recommend that it should be accomplished within a time frame, from the first medical contact (FMC) to the first device, of less than 90 minutes and preferably within 60 minutes in patients who present within 12 hours of the onset of symptoms (Class 1A) (Figure 2.2). To achieve this goal, it is recommended that all communities create and maintain a regional system of care with integrated emergency medical services (EMS) and hospital systems that meet the guidelines for rapid diagnosis and triage (Class 1B). Patients should be transferred by EMS to PCI-capable hospitals for primary PCI. When a patient presents at a non-PCI-capable hospital, immediate transfer to a PCI-capable hospital should be done as rapidly as possible, with a goal of 120 minutes from the FMC to device use (Class 1B) and a door-in to door-out time at the first hospital of 30 minutes or less. When the FMC-to-device time is anticipated to be more than 120 minutes, a fibrinolytic agent should be given first unless it is contraindicated. It is reasonable to then transfer the patient for PCI within 3 to 24 hours (the so-called pharmacoinvasive strategy) (Class 2a [B]). When this strategy is chosen, the fibrinolytic agent should be administered within 30 minutes of hospital arrival. The guideline class of recommendation (COR) and LOE for these primary PCI strategies are shown in Figures 2.2 to 2.5.

The management of patients with cardiogenic shock or severe heart failure is more aggressive with recommendations for PCI (or coronary artery bypass grafting [CABG] when PCI is not feasible), regardless of the time after the onset of the symptoms or first contact. In this setting, urgent transfer to a PCI-capable hospital is critical. Transfer for a failure of fibrinolytic therapy is the recommended strategy (so-called rescue angioplasty) (Class 1, C-LD).

The national efforts to improve ischemic time (symptom onset to device or drug) have focused on the FMC-to-device time and particularly a key component of this time—the door-to-device time (D2D). Public reporting and efforts such as the AHA's Mission Lifeline program and the ACCF's D2B program have been successful in improving D2D times.¹⁰ The strategies to achieve this reduction have included pre-hospital electrocardiography (ECG) and activation of the cath lab while in route to the hospital, emergency department (ED) activation of the PCI team, a single page for activation of the cath lab, less than 20 minutes until the cath lab staff arrive, and timely feedback to the STEMI care team.¹¹ Although these measures have been effective, the greatest delay in reperfusion is often the delay between the onset of symptoms to the 911 call or the hospital arrival. There are many reasons for this delay, and unfortunately, national efforts to reduce this time have not been successful.¹²

When the patient arrives at the cath lab, the interventional procedure should be performed expeditiously.

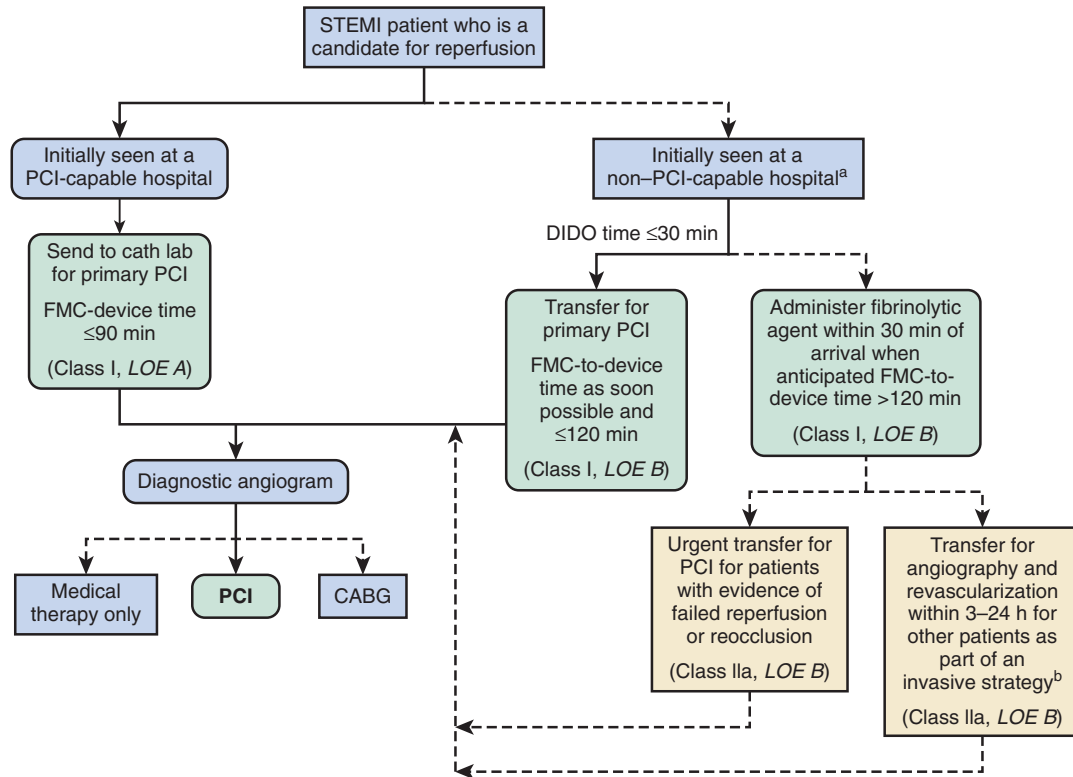


FIGURE 2.2 Acute management for patients with ST-segment elevation myocardial infarction (STEMI). CABG, coronary artery bypass grafting; DIDO, door in door out; FMC, first medical contact; LOE, level of evidence; PCI, percutaneous coronary intervention. (Used with permission from O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. 2013;127:e362-e425.)

COR	LOE	Recommendations
1	A	1. In patients with STEMI and ischemic symptoms for <12 h, PCI should be performed to improve survival.
1	B-R	2. In patients with STEMI and cardiogenic shock or hemodynamic instability, PCI or CABG (when PCI is not feasible) is indicated to improve survival, irrespective of the time delay from MI onset.
1	B-NR	3. In patients with STEMI who have mechanical complications (e.g., ventricular septal rupture, mitral valve insufficiency because of papillary muscle infarction or rupture, or free wall rupture), CABG is recommended at the time of surgery, with the goal of improving survival.
1	C-LD	4. In patients with STEMI and evidence of failed reperfusion after fibrinolytic therapy, rescue PCI of the infarct artery should be performed to improve clinical outcomes.
2a	B-R	5. In patients with STEMI who are treated with fibrinolytic therapy, angiography within 3 to 24 h with the intent to perform PCI is reasonable to improve clinical outcomes.
2a	B-NR	6. In patients with STEMI who are stable and presenting 12 to 24 h after symptom onset, PCI is reasonable to improve clinical outcomes.
2a	B-NR	7. In patients with STEMI in whom PCI is not feasible or successful, with a large area of myocardium at risk, emergency or urgent CABG can be effective as a reperfusion modality to improve clinical outcomes.
2a	C-EO	8. In patients with STEMI complicated by ongoing ischemia, acute severe heart failure, or life-threatening arrhythmia, PCI can be beneficial to improve clinical outcomes, irrespective of time delay from MI onset.
3: No benefit	B-R	9. In asymptomatic stable patients with STEMI who have a totally occluded infarct artery >24 h after symptom onset and are without evidence of severe ischemia, PCI should not be performed.
3: Harm	C-EO	10. In patients with STEMI, emergency CABG should not be performed after failed primary PCI: • In the absence of ischemia or a large area of myocardium at risk, or • If surgical revascularization is not feasible because of a no-reflow state or poor distal targets.

FIGURE 2.3 Recommendations for revascularization of the infarct artery in ST-segment elevation myocardial infarction (STEMI). See text for descriptions of levels of evidence (LOEs). CABG, coronary artery bypass grafting; COR, class of recommendation; MI, myocardial infarction; PCI, percutaneous coronary intervention. (Used with permission from Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(2):e21-e129.)

COR	LOE	Recommendations
1	A	1. In selected hemodynamically stable patients with STEMI and multivessel disease, after successful primary PCI, staged PCI of a significant noninfarct artery stenosis is recommended to reduce the risk of death or MI.
2a	C-EO	2. In selected patients with STEMI with complex multivessel noninfarct artery disease, after successful primary PCI, elective CABG is reasonable to reduce the risk of cardiac events.
2b	B-R	3. In selected hemodynamically stable patients with STEMI and low-complexity multivessel disease, PCI of a noninfarct artery stenosis may be considered at the time of primary PCI to reduce cardiac event rates.
3: Harm	B-R	4. In patients with STEMI complicated by cardiogenic shock, routine PCI of a noninfarct artery at the time of primary PCI should not be performed because of the higher risk of death or renal failure.

FIGURE 2.4 Recommendations for revascularization of noninfarct artery in ST-segment elevation myocardial infarction (STEMI). See text for descriptions of levels of evidence (LOEs). CABG, coronary artery bypass grafting; COR, class of recommendation; MI, myocardial infarction; PCI, percutaneous coronary intervention. (Used with permission from Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;79(2):e21-e129.)

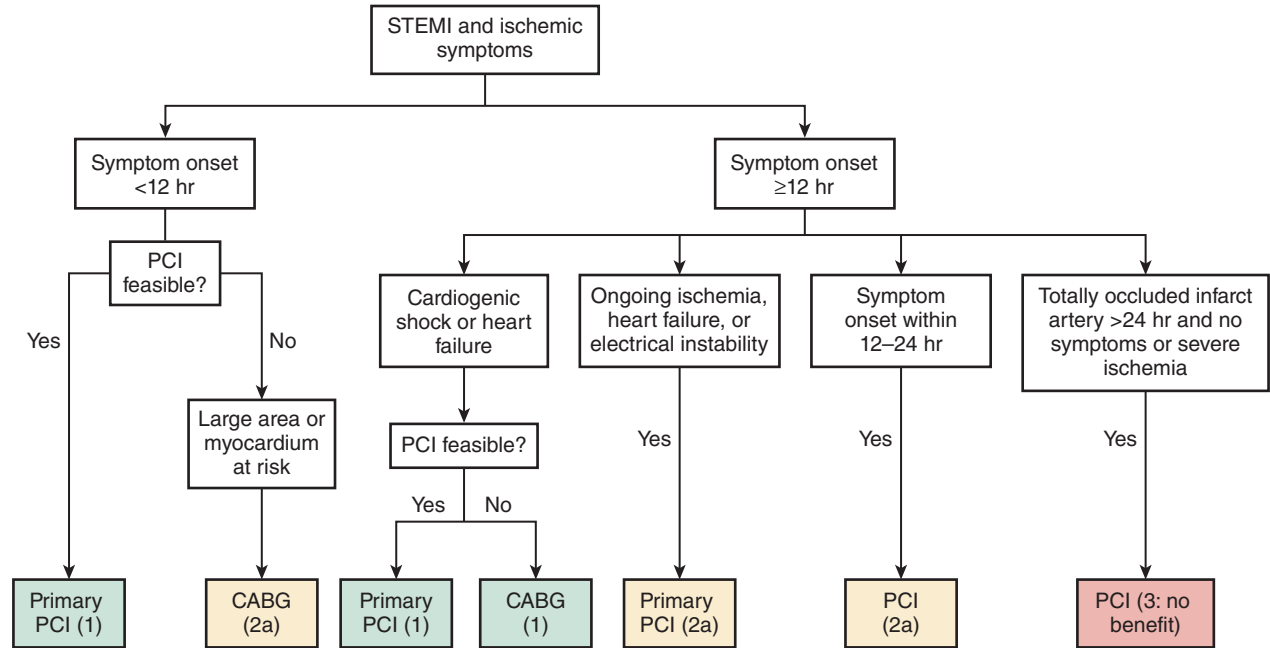


FIGURE 2.5 Indications for revascularization in ST-segment elevation myocardial infarction (STEMI) without fibrinolysis. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention. (Used with permission from Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;79(2):e21-e129.)

Antiplatelet and anticoagulant therapy should be given as soon as possible on initial medical contact. Dual antiplatelet therapy (aspirin and prasugrel or ticagrelor in preference to clopidogrel) and an anticoagulant (unfractionated heparin [UFH] or bivalirudin) should be administered. Glycoprotein (GP) IIb/IIIa agents (abciximab, tirofiban, or eptifibatide) are reasonable when a large thrombus, no reflow, or slow flow (Class 2a, B-R). In current practice, the use of GP IIb/IIIa agents has decreased because of concerns about increased bleeding risk, the introduction of the newer more potent P₂Y₁₂ antiplatelet agents, and the greater use of bivalirudin.¹³ Based on randomized trials,^{14,15} the current guidelines do not recommend thrombectomy before primary PCI (Class 3A).^{7,8} Drug-eluting stents (DESs) are recommended over bare-metal stents because of the reduction in target vessel revascularization without an increased risk of stent thrombosis.^{7,16} Initial primary PCI should be restricted to the infarct-related

artery, and in multivessel disease, PCI of the noninfarct artery is recommended in patients as a staged procedure (Class 1A) with complete revascularization the preferred strategy.^{7,8} In selected hemodynamically stable patients, noninfarct lesions may be considered at the time of primary PCI (Class 2b). In patients with STEMI and cardiogenic shock, routine PCI of the noninfarct artery at the time of primary PCI should not be done (Class 3).⁷ Multivessel PCI is also indicated in patients who develop spontaneous symptoms of ischemia (Class 1C) after primary PCI and patients with an intermediate to high risk of non-invasive testing before discharge (Class 2a).

Coronary artery bypass surgery is indicated for patients not amenable to PCI and those who have ongoing or recurrent ischemia, cardiogenic shock, severe heart failure, or other high-risk features (Class 1B). CABG is rarely used as the primary reperfusion strategy, but it is commonly used for other indications during hospitalization,

particularly in patients who have extensive coronary disease or have disease that is not amenable to PCI.

The subsequent medical management with dual antiplatelet therapy, oral anticoagulants, beta-blockers, angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, and statins, in addition to risk factor modification and cardiac rehabilitation, are critically important in improving long-term outcomes and preventing future events. Readers should refer to the 2013 ACC/AHA STEMI guidelines, 2021 ACC/AHA coronary revascularization guidelines, and 2018 ESC/EACTS myocardial revascularization guidelines for specific recommendations.⁷⁻⁹

Guidelines for Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction

The ACCF/AHA guidelines for unstable angina (UA) and non-ST-segment elevation MI (NSTEMI) were released in 2007 followed by two focused updates with the last focused update in 2012.¹⁷⁻¹⁹ The 2018 ESC/EACTS guidelines for myocardial revascularization provide more current recommendations, and the most current

recommendations are in the 2021 ACC AHA coronary revascularization guidelines.^{7,8}

The initial assessment of a patient with prolonged or crescendo chest pain is done to determine the likelihood of acute coronary syndrome based on the history, physical examination, ECG, laboratory tests, cardiac biomarkers, and risk factors. The initial assessment of acute chest pain in the ED should be to assess the likelihood of possible ACS or nonischemic causes. The 2021 AHA/ACC/ASE guidelines for evaluation and diagnosis of chest pain guidelines provide guidance in the decision making²⁰ (Figure 2.6). If the patient is believed to have possible acute coronary syndrome (ACS), the troponin level should be obtained, and it is recommended that clinical decision pathways be used for further risk assessment. Refer to this guideline for more details. The risk assessment should use one of the available risk scores such as Thrombolysis in Myocardial Infarction (TIMI) or Global Registry of Acute Coronary Events (GRACE) or Heart Score (Class 2a [B]). Patients at low risk or low likelihood of ACS can be managed in the ED, a chest pain unit or in the hospital. The patient can be further evaluated in the outpatient setting with a noninvasive test

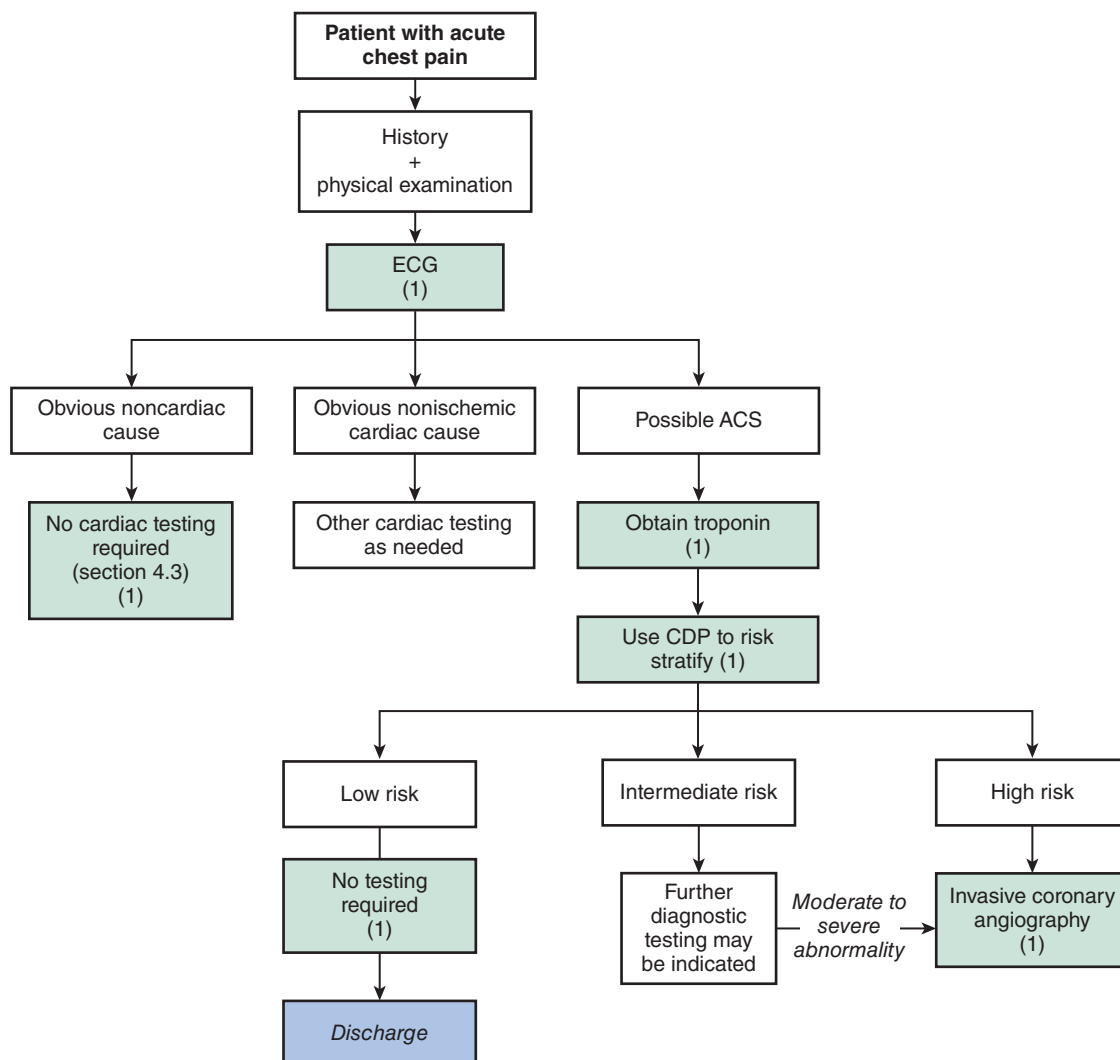


FIGURE 2.6 Management of acute chest pain. ACS, acute coronary syndrome; CDP, clinical decision pathway; ECG, electrocardiography. (Reprinted with permission Circulation. 2021;144:e368-e454 © 2021 American Heart Association, Inc.)



such as a treadmill exercise test, a nuclear imaging stress test, or coronary computed tomography angiography.

Intermediate-risk patients should have further diagnostic testing, and if they have a moderate or severe abnormality on noninvasive testing, the patient should be considered for invasive coronary angiography. The testing and decision process is shown in [Figure 2.7](#).²⁰

Patients at high risk after initial assessment should have aggressive medical therapy and invasive coronary angiography. It is important to note that cardiac enzyme elevation alone does not automatically imply high risk and can be due to causes other than a myocardial infarction (MI); likewise, a patient can be high risk without elevation of cardiac enzymes.^{20,21}

The timing of the invasive strategy in high-risk patients should be determined by the degree of risk. The 2018 ESC/EACTS guidelines recommend that coronary angiography and revascularization in patients with Non ST-Acute Coronary syndrome (NST-ACS) be done immediately (within 2 hours) if the patient is at very high risk and early (within 24 hours) if the patient is at high risk or delayed (within 72 hours) in patients with intermediate risk⁸ ([Figure 2.8](#)). The largest clinical trial to examine the timing of invasive strategy in ACS was the TIMAC trial. Although it failed to reach its primary endpoint, it strongly suggested that an invasive strategy should be performed within 12 to 24 hours, particularly in those patients at highest risk, as determined by the GRACE score (Class 2a [B]).²²

The 2021ACC/AHA/SCAI coronary revascularization guidelines recommendations for coronary angiography and revascularization in NST-ACS are shown in [Figure 2.9](#).⁷

All patients should be given anticoagulant therapy in addition to antiangina medication. The ACC/AHA guideline recommendations for antiplatelet and anticoagulant agents in patients undergoing PCI are shown in [Figure 2.10](#).⁷ It is recommended that aspirin be given as soon as possible (or clopidogrel if the patient is allergic to aspirin) (Class IA). Those at moderate to high risk of NSTEMI or in whom an initial invasive strategy has been chosen should be given dual antiplatelet therapy on presentation (Class IA) with a loading and maintenance dose of clopidogrel or ticagrelor or prasugrel. If not given before PCI, clopidogrel, ticagrelor, and prasugrel can be given at the time of the PCI procedure. The use of GP IIb/IIIa inhibitors in patients with ACS undergoing PCI should be restricted to those with a large thrombus burden, no reflow, or slow flow (Class 2A). Studies have shown that upstream use of GP IIb/IIIa inhibitors is not useful. The anticoagulants available are UFH, enoxaparin, fondaparinux, and bivalirudin. For patients undergoing PCI, UFH is recommended (Class 1C). Bivalirudin is a reasonable alternative (Class 2B). Fondaparinux and enoxaparin in patients who are managed with a conservative strategy can be continued when they undergo an invasive procedure. Switching from enoxaparin to heparin has not recommended because of increased bleeding. If fondaparinux is used, UFH should be given in addition if the patient undergoes a PCI because of an increased risk of catheter thrombosis (Class 1B). Cangrelor may be considered in P₂Y₁₂ receptor inhibitor-naïve patients undergoing PCI (Class 2b [A]).

Certain subgroups of patients are at higher risk and need special consideration. Patients with diabetes are well

recognized to be at greater risk for short- and long-term adverse events with ACS. The results of randomized trials suggest that the choice of an initial invasive or conservative management strategy in patients with ACS should be similar to that for patients without diabetes (Class 1A). However, the guidelines recommend CABG rather than PCI for patients with multivessel disease with left anterior descending coronary artery (LAD) involvement needing revascularization (Class 1A). The results of the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, which specifically compared DES with CABG in patients with diabetes, showed superior outcomes with CABG in all subgroups of patients and strongly supported the guideline recommendations.²³ There is evidence that patients with chronic kidney disease are at greater risk for short- and long-term complications of revascularization. The guidelines recommend that an invasive strategy is reasonable for patients with CKD who are at high risk (Class 2a [B]). Because contrast nephropathy can increase the risk of patients undergoing invasive procedures, the guidelines recommend that all patients have a calculation of creatinine clearance before PCI and those with CKD have adequate hydration before coronary angiography and PCI (Class 1B). Readers should refer to the 2007 and 2012 ACCF/AHA guidelines for UA/NSTEMI, the 2021 ACC AHA coronary revascularization guidelines, and the 2018 ESC/EACTS guidelines for more details concerning the early and late management of these patients.^{7,8,17-19}

Guidelines for Stable Ischemic Heart Disease

The 2002, 2007, and 2012 ACCF/AHA guidelines for stable ischemic heart disease (SIHD) with the 2021 coronary artery revascularization guidelines, the ESC/EACTS myocardial revascularization guidelines, and the 2021 AHA/ACC guidelines for the evaluation and diagnosis of chest pain provide the past and most current recommendations.^{7,8,20,24-26}

The guidelines recommend that patients with known or suspected SIHD should be initially risk stratified using history, clinical factors, ECG, and an exercise or cardiac imaging study. In addition to determining the likelihood of obstructive coronary disease, exercise testing provides valuable information concerning exercise capacity that can further help in risk stratification and management. The 2021AHA/ACC chest pain guidelines provide a detailed discussion of the best noninvasive method to evaluate patients with SIHD, and this document should be referred to for more information on how to choose the proper test.²⁰ A clinical decision pathway for patients with stable chest pain and no known coronary artery disease (CAD) is shown in [Figure 2.11](#). The two exceptions to obtaining a noninvasive test first are patients with sudden cardiac death or life-threatening ventricular arrhythmias and those with known SIHD who develop signs and symptoms of heart failure, in which coronary angiography should be the initial risk-stratifying test (Class 1B). Patients with a prior MI, pathological Q waves, signs or symptoms of heart failure, complex ventricular arrhythmias, or an undiagnosed heart murmur should undergo an assessment of

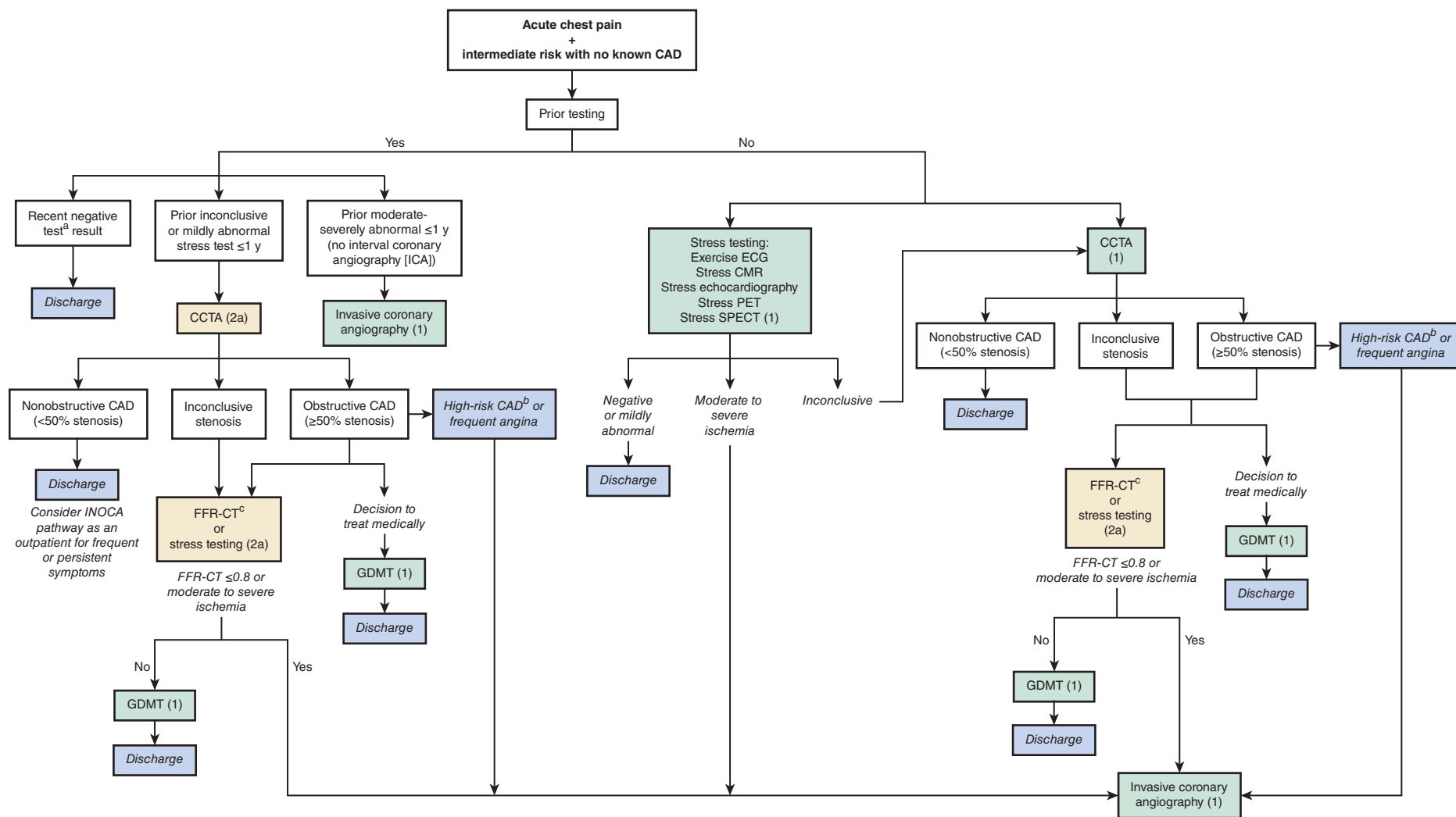


FIGURE 2.7 Management of patients with acute chest pain and intermediate risk. CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; ECG, electrocardiography; FFR-CT, fractional flow reserve computed tomography; GDMT, guideline-directed medical therapy; INOCA, ischemia in nonobstructive coronary arteries; PET, positron emission tomography; SPECT, single-photon emission computed tomography. (Reprinted with permission Circulation. 2021;144:e368-e454 © 2021 American Heart Association, Inc.)

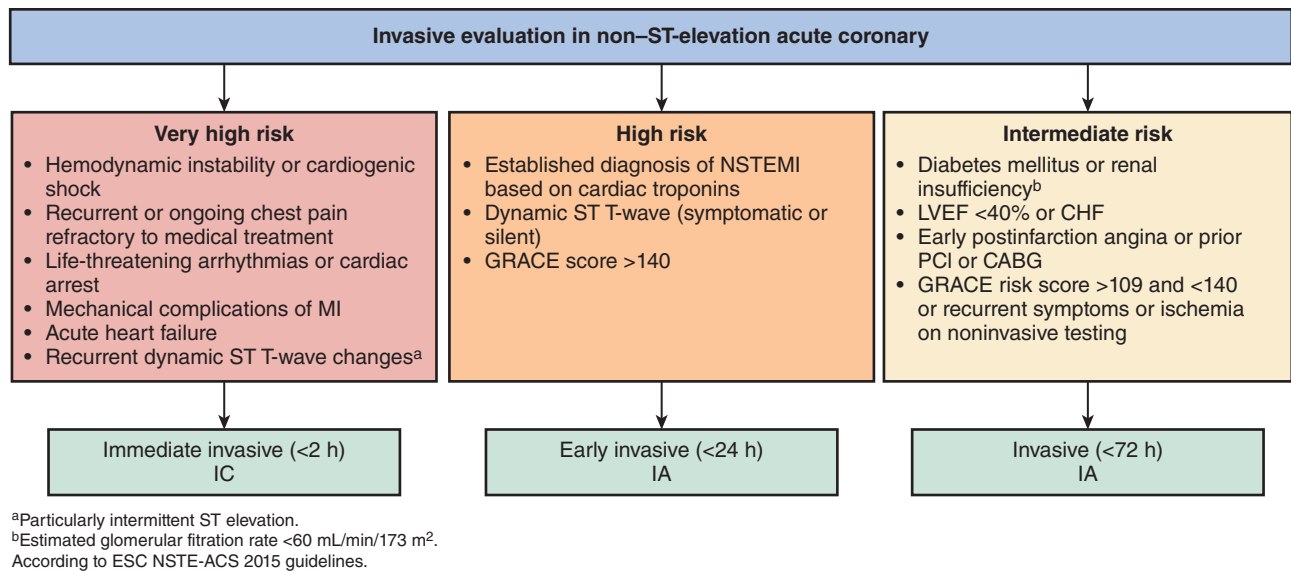


FIGURE 2.8 Timing of percutaneous coronary intervention (PCI) in non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) according to risk stratification. CABG, coronary artery bypass grafting; ESC, European Society of Cardiology; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention. (Used with permission from Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87-165.)

COR	LOE	Recommendations
1	A	1. In patients with NSTEMI-ACS who are at elevated risk of recurrent ischemic events and are appropriate candidates for revascularization, an invasive strategy with the intent to proceed with revascularization is indicated to reduce cardiovascular events.
1	B-R	2. In patients with NSTEMI-ACS and cardiogenic shock who are appropriate candidates for revascularization, emergency revascularization is recommended to reduce the risk of death.
1	C-LD	3. In appropriate patients with NSTEMI-ACS who have refractory angina or hemodynamic or electrical instability, an immediate invasive strategy with intent to perform revascularization is indicated to improve outcomes.
2a	B-R	4. In patients with NSTEMI-ACS who are initially stabilized and are at high risk of clinical events, it is reasonable to choose an early invasive strategy (within 24 h) over a delayed invasive strategy to improve outcomes.
2a	B-R	5. In patients with NSTEMI-ACS who are initially stabilized and are at intermediate or low risk of clinical events, an invasive strategy with intent to perform revascularization is reasonable before hospital discharge to improve outcomes.
2a	B-NR	6. In patients with NSTEMI-ACS who have failed PCI and have ongoing ischemia, hemodynamic compromise, or threatened occlusion of an artery with substantial myocardium at risk who are appropriate candidates for CABG, emergency CABG is reasonable.
3: Harm	B-R	7. In patients with NSTEMI-ACS who present in cardiogenic shock, routine multivessel PCI of non culprit lesions in the same setting should not be performed.

FIGURE 2.9 Recommendations for an invasive strategy in acute coronary syndrome (ACS). See text for descriptions of levels of evidence (LOEs). CABG, coronary artery bypass grafting; COR, class of recommendation; NSTEMI, non-ST-segment elevation; PCI, percutaneous coronary intervention. (Used with permission from Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(2):e21-e129.)

left ventricular (LV) systolic and diastolic myocardial function, and an assessment of pericardial and valve structures is recommended (Class 1B). This is most commonly obtained with two-dimensional echocardiography.

If the patient does not have any high-risk features on noninvasive testing, an initial trial of medical therapy should be started before coronary angiography is considered. Medical therapy should include antianginal medication, lifestyle changes (diet and exercise), and modification of coronary risk factors (hypertension, dyslipidemia, cigarette smoking). In those with high-risk features on noninvasive

therapy, further risk stratification should be done with coronary angiography to determine the extent of coronary disease (Class 1B).

Revascularization decisions are based on two primary indications: whether CABG or PCI will improve survival and whether revascularization will improve severe ischemic symptoms not adequately treated with initial medical therapy. It is recommended that a heart team approach be used in making revascularization decisions for patients with left main or complex CAD (Class 1C). Measurement of Society of Thoracic Surgery (STS) and Synergy between

ANTIPLATELET

COR	LOE	Recommendations
1	B-R	1. In patients undergoing PCI, a loading dose of aspirin, followed by daily dosing, is recommended to reduce ischemic events. ^a
1	B-R	2. In patients with ACS undergoing PCI, a loading dose of P2Y12 inhibitor, followed by daily dosing, is recommended to reduce ischemic events.
1	C-LD	3. In patients with SIHD undergoing PCI, a loading dose of clopidogrel, followed by daily dosing, is recommended to reduce ischemic events.
1	C-LD	4. In patients undergoing PCI within 24 hours after fibrinolytic therapy, a loading dose of 300 mg of clopidogrel, followed by daily dosing, is recommended to reduce ischemic events.
2a	B-R	5. In patients with ACS undergoing PCI, it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel to reduce ischemic events, including stent thrombosis.
2b	B-R	6. In patients <75 years of age undergoing PCI within 24 hours after fibrinolytic therapy, ticagrelor may be a reasonable alternative to clopidogrel to reduce ischemic events.
3: Harm	B-R	7. In patients undergoing PCI who have a history of stroke or transient ischemic attack, prasugrel should not be administered.
COR	LOE	Recommendations
2b	B-R	1. In patients undergoing PCI who are P2Y12 inhibitor naïve, intravenous cangrelor may be reasonable to reduce periprocedural ischemic events.
COR	LOE	Recommendations
2a	C-LD	1. In patients with ACS undergoing PCI with large thrombus burden, no-reflow, or slow flow, intravenous glycoprotein IIb/IIIa inhibitor agents are reasonable to improve procedural success.
3: No benefit	B-R	2. In patients with SIHD undergoing PCI, the routine use of an intravenous glycoprotein IIb/IIIa inhibitor agent is not recommended.

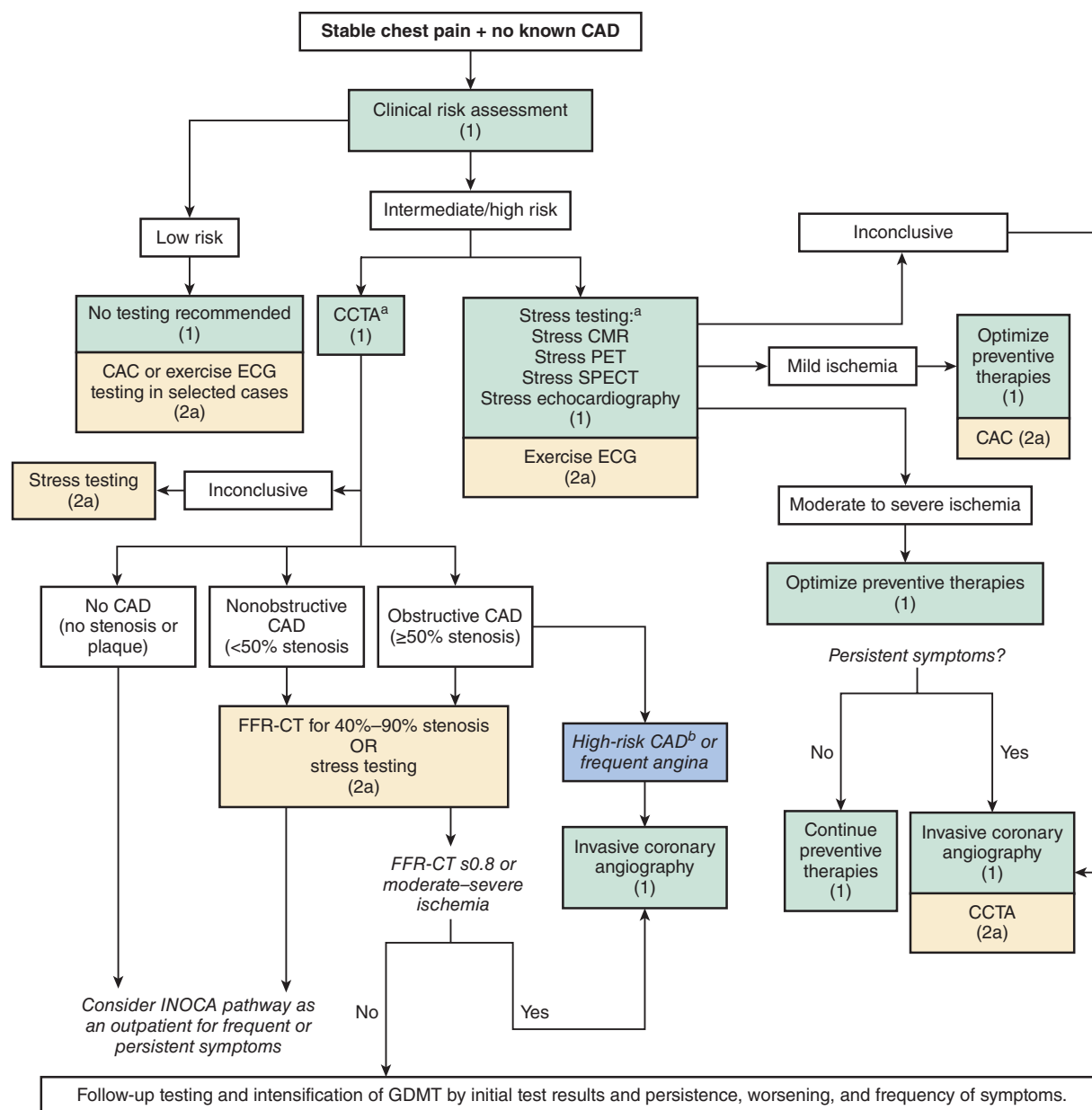
ANTICOAGULANT

COR	LOE	Recommendations
1	C-EO	1. In patients undergoing PCI, administration of IV UFH is useful to reduce ischemic events.
1	C-LD	2. In patients with HIT undergoing PCI, bivalirudin or argatroban should be used to replace UFH to avoid thrombotic complications.
2b	A	3. In patients undergoing PCI, bivalirudin may be a reasonable alternative to UFH to reduce bleeding.
2b	B-R	4. In patients treated with upstream subcutaneous enoxaparin for unstable angina or NSTEMI-ACS, the use of IV enoxaparin may be considered at the time of PCI to reduce ischemic events.
3: Harm	B-R	5. In patients on therapeutic SC enoxaparin in whom the last dose was administered within 12 h of PCI, UFH should not be used for PCI and may increase bleeding.

FIGURE 2.10 Antiplatelet and anticoagulant therapy in patients undergoing percutaneous coronary intervention (PCI). See text for descriptions of levels of evidence (LOEs). COR, class of recommendation; HIT, heparin-induced thrombocytopenia; IV, intravenous; NSTEMI-ACS, non-ST-segment elevation acute coronary syndrome; UFH, unfractionated heparin; SC, subcutaneous. (Used with permission from Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;79(2):e21-e129.)

PCI with Taxus and Cardiac Surgery (SYNTAX) trial, scores is also recommended to assist in this decision making. The optimal choice in an individual patient requires a careful balance of the risks and benefits of each technique and medical therapy alone.

The specific revascularization recommendations for with PCI or CABG are shown in [Figure 2.12](#). The guideline recommendations for revascularization to improve survival include unprotected left main, three-vessel disease, or those with two-vessel disease and a proximal LAD lesion



^aTest choice guided by patient's exercise capacity, resting electrocardiographic abnormalities; CCTA preferable in those <65 years of age and not on optimal preventive therapies; stress testing favored in those ≥65 years of age (with a higher likelihood of ischemia).

^bHigh-risk CAD means left main stenosis ≥50%; anatomically significant 3-vessel disease (≥70% stenosis).

FIGURE 2.11 Clinical decision pathway for patients with stable chest pain and no known coronary artery disease (CAD). CAC, coronary artery calcification; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; ECG, electrocardiography; FFR-CT, fractional flow reserve computed tomography; GDMT, guideline-directed medical therapy; PET, positron emission tomography; SPECT, single-photon emission computed tomography. (Reprinted with permission Circulation. 2021;144:e368-e454 © 2021 American Heart Association, Inc.)

and those with reduced LV dysfunction. In these settings, CABG is favored over PCI (Class 1B vs 2a [A] for PCI). This is in part because of limited studies comparing PCI with medical therapy in multivessel disease and the lower mortality rate with CABG compared with PCI in patients with three-vessel disease.

Revascularization to improve symptoms can be accomplished with either CABG or PCI, with CABG favored in those with complex disease (e.g., SYNTAX score >22) and PCI favored in those with prior CABG (Class 2a).

The presence of diabetes is an important consideration in determining the optimal revascularization technique. Randomized trials and a meta-analysis have shown a

mortality advantage for CABG over PCI in patients with multivessel disease and diabetes.²⁷ The FREEDOM trial randomized patients with multivessel disease to PCI with DESs or to CABG. The study demonstrated a lower rate of death and MI with CABG. There was no reduction in cardiovascular death alone.²³ The trial also found no relationship between the SYNTAX score and outcome. Conversely, the SYNTAX trial did not find an independent effect of diabetes on outcome but found a strong relationship with the SYNTAX score.²⁸ The differences in outcomes in these studies may be attributable to differences in the extent of disease included in each trial. In the 2021 ACC/AHA coronary revascularization guidelines, the use of the SYNTAX

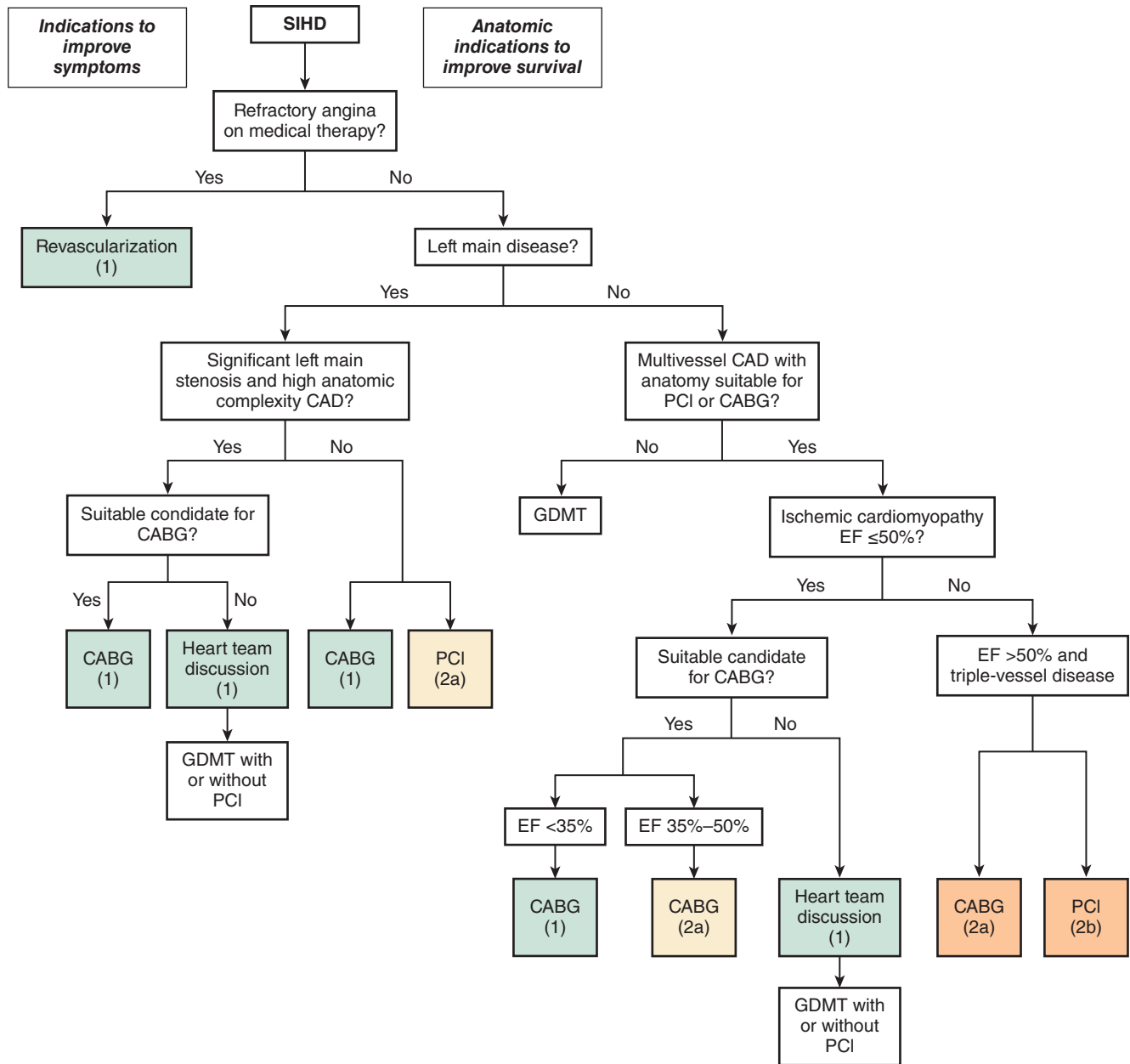


FIGURE 2.12 Revascularization in patients with stable ischemic heart disease (SIHD). CABG, coronary artery bypass grafting; CAD, coronary artery disease; EF, ejection fraction; GDMT, guideline-directed medical therapy; PCI, percutaneous coronary intervention. (Used with permission from Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;79(2):e21-e129.)

score in patients with multivessel disease may be useful to guide revascularization (Class 2b, B-NR).⁷

The management of patients after a successful revascularization procedure is critically important. Periodic follow-up should be done at least annually, with assessment of symptoms and functional status; adequacy of medical therapy; presence of complications, including heart failure and arrhythmias; and optimal treatment of risk factors and lifestyle changes (Class 1C). Noninvasive testing should be done in those with recurrent symptoms consistent with UA (Class 1B) and those with at least moderate functional limitation or known or likely multivessel disease (Class 2a [B]). In general, an exercise test or exercise with nuclear myocardial perfusion imaging or echocardiography is preferred.

APPROPRIATENESS CRITERIA

Development Process

The ACCF/AHA guidelines have provided a solid foundation for many areas of clinical practice, but there remain many clinical situations for which there are no guidelines. Even when guidelines are available, they are often based on limited clinical trials or registry data. A study of the ACC/AHA guidelines has shown that Class I recommendations make up only 30% of the guideline recommendations, and of these, only one-third were based on Level A evidence.⁶ Almost half of all recommendations were based on expert opinion (Level C). Another limitation is that they often fail to take into consideration the multiple factors that are weighed in clinical decision making. For instance,



age, sex, degree of symptoms, extent of disease, and suitability and risk of PCI or CABG are usually considered when making decisions about revascularization.

Appropriateness criteria have been developed to address these limitations of guidelines and concerns about the documented wide variability in the use of invasive procedures in practice (including both overuse and underuse). Appropriateness criteria are best applied to diagnostic or therapeutic procedures. The development of the criteria used a Modified Delphi process created by the RAND Corporation. A committee of experts reviews the evidence, including guidelines and observational and randomized trials and determines the key factors that should be considered in decision making in the use of a test. The committee constructs all the possible combinations of these factors and ranks the evidence supporting use of the procedure in each clinical situation as “appropriate,” “indeterminate,” or “inappropriate.” More recently, these terms have been changed to “appropriate care,” “may be appropriate care,” and “rarely appropriate care.” As with guidelines, the criteria are externally reviewed and approved by the sponsoring organizations.

Summary of Recommendations for Coronary Revascularization

The ACCF/SCAI/STS/AATS/AHA/American Society of Nuclear Cardiology (ASNC) appropriateness criteria for coronary revascularization were published in 2009 and updated in 2012.^{29,30} In the most recent document, five factors were used to develop more than 180 separate clinical scenarios. These factors were the clinical presentation (ACS or SIHD), severity of angina (Canadian Cardiovascular Society class), extent of ischemia on noninvasive testing, extent of medical therapy, and extent of anatomic disease (left main, one-, two-, or three-vessel disease with and without a proximal LAD lesion). The committee rated each scenario as appropriate, uncertain, or inappropriate using a score ranging from 1 to 8. The ratings for patients with nonacute indications (SIHD) are shown in [Figure 2.13](#). Please refer to the primary document for all the appropriateness criteria. In patients with mild symptoms or no or minimal antianginal therapy, single- or double-vessel disease, and low risk on noninvasive testing, the committee thought it was inappropriate to do PCI. Conversely, it was appropriate in all groups if there was severe angina (Canadian Cardiovascular Society Class II–IV) as long as PCI could be done (lack of a chronic total occlusion) or the stress test was low risk.

Using these criteria, Chan et al.³¹ examined the frequency of appropriate indications for PCI from more than 500,000 PCI procedures in the National Cardiovascular Data Registry. They found that the majority of patients with acute indications (largely ACS) were appropriate (98.6%), but only 50.4% of nonacute indications (largely SIHD) were appropriate, and 11.6% were inappropriate. Others have shown that as much as 25% of patients with SIHD did not have an indication for the procedure that was considered by guidelines as appropriate.³² The study by Chan et al.³¹ also demonstrated great variability in the frequency of inappropriate indications from one hospital to another (6%–16.7% interquartile range), suggesting that opportunities

exist to improve quality. One of the most common reasons for an inappropriate procedure was the presence of mild symptoms or no symptoms, no noninvasive assessment or low risk, and no medical therapy.

The strength of the criteria is that they more accurately reflect practice by considering a number of key factors in the decision for a specific procedure. However, despite consideration of up to five factors, they still do not account for all the factors that may sway a decision one way or another in a specific patient.³³ In addition, they are derived from an expert panel that relies on expert opinion in a large majority of the criteria.³⁴ This leads to less confidence that the criteria are representative of practice and reproducible. One study demonstrated significant variability (up to twofold) in the appropriateness classifications between two panels of experts using the same evidence for cardiac catheterization.³⁵ The criteria have led to better understanding of the use of procedures in practice and can help to develop better systems to reduce variability. They have also been used during pretest screening to reduce variability. However, because of the lower reliability of the criteria, they should not be used as a basis for reimbursement.

OTHER METHODS TO IMPROVE QUALITY

Performance Measures

Performance measures are selected quality metrics that are evidence based, interpretable, definable, actionable, reliable, valid, and feasible to be collected and reported. They are best used to measure quality and compare outcomes among different institutions, and they have been used in public reporting.³⁶ Accordingly, they are usually few in number. Recently, the ACCF/AHA/SCAI/AMA-Convended Primary Care Information Project /National Committee for Quality Assurance 2013 Performance Measure for Adults Undergoing Percutaneous Coronary Intervention was published.³⁷ The prior performance measures in cardiology were focused on acute MI and congestive heart failure (CHF), and the 2013 measures were the first to directly address PCI performance. The committee identified 10 measures that were determined to meet the criteria and to have a high impact on improving quality ([Table 2.1](#)). The dimensions of care ranged from diagnostics, patient education, and treatment. Only one, cardiac rehabilitation referral, also involved patient self-management and monitoring of disease. A detailed description and rationale for choosing these criteria are available in the references.

Although many of the performance measures for PCI are designated for internal quality control, others are intended for monitoring of hospital quality and comparisons among hospitals. If accurate data can be collected on all measures, then they will be used to assess hospital quality in the future.

Centers for Medicare & Medicaid Services and insurance companies have used the established performance measures for acute MI and CHF for pay-for-performance (P4P) financial incentives. Studies to date have failed to show whether P4P actually improves care and quality beyond what is occurring because of other efforts.³⁸ In addition, it

Low-risk findings on noninvasive study						Asymptomatic					
Symptoms: medical Rx						Stress test: med Rx					
Class III or IV: max Rx	U	A	A	A	A	High risk: max Rx	U	A	A	A	A
Class I or II: max Rx	U	U	A	A	A	High risk: no or min Rx	U	U	A	A	A
Asymptomatic: max Rx	I	I	U	U	U	Int risk: max Rx	U	U	U	U	A
Class III or IV: no or min Rx	I	U	A	A	A	Int risk: no or min Rx	I	I	U	U	A
Class I or II: no or min Rx	I	I	U	U	U	Low risk: max Rx	I	I	U	U	U
Asymptomatic: no or min Rx	I	I	U	U	U	Low risk: no or min Rx	I	I	U	U	U
Coronary anatomy	CTO of 1 vz; no other disease	1- to 2-vz disease; no prox LAD	1-vz disease of prox LAD	2-vz disease with prox LAD	3-vz disease; no left main	Coronary anatomy	CTO of 1 vz; no other disease	1- to 2-vz disease; no prox LAD	1-vz disease of prox LAD	2-vz disease with prox LAD	3-vz disease; no left main

Intermediate-risk findings on noninvasive study						CCS Class I or II angina					
Symptoms: medical Rx						Stress test: med Rx					
Class III or IV: max Rx	A	A	A	A	A	High risk: max Rx	A	A	A	A	A
Class I or II: max Rx	U	A	A	A	A	High risk: no or min Rx	U	A	A	A	A
Asymptomatic: max Rx	U	U	U	U	A	Int risk: max Rx	U	A	A	A	A
Class III or IV: no or min Rx	U	U	A	A	A	Int risk: no or min Rx	U	U	U	A	A
Class I or II: no or min Rx	U	U	U	A	A	Low risk: max Rx	U	U	A	A	A
Asymptomatic: no or min Rx	I	I	U	U	A	Low risk: no or min Rx	I	I	U	U	U
Coronary anatomy	CTO of 1 vz; no other disease	1- to 2-vz disease; no prox LAD	1-vz disease of prox LAD	2-vz disease with prox LAD	3-vz disease; no left main	Coronary anatomy	CTO of 1 vz; no other disease	1- to 2-vz disease; no prox LAD	1-vz disease of prox LAD	2-vz disease with prox LAD	3-vz disease; no left main

A

FIGURE 2.13 Appropriateness criteria for nonacute indications. **(A)** Low and intermediate risk on noninvasive study. **(B)** High risk on non-invasive study. A, Appropriate; CCS, Canadian Cardiovascular Society; CTO, chronic total occlusion; *int*, intermediate; LAD, left anterior descending coronary artery; *max*, maximum; *min*, minimum; *prox*, proximal; *Rx*, prescription; *U*, Uncertain; *vz*, vessel. (Used with permission from Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation appropriate use criteria task force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and The Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol*. 2012;59:857-881.)

is not clear whether P4P has reduced unnecessary procedures and hospital and health care costs. Future studies are needed to determine whether P4P is an effective method to improve quality.

Public Reporting

Many states publicly report risk-adjusted cardiac surgical outcomes by hospital. The goal is to provide information to the public so individuals can make informed decisions

about where to get the best care and to improve quality by incenting hospitals with high mortality rates to improve outcomes. The public reporting of PCI outcomes has only recently been instituted.³⁹ Whether public reporting can reduce cost and mortality is uncertain. Data from three states with public reporting of PCI (New York, Pennsylvania, and Massachusetts) have shown that the rates of PCI for acute MI were less than in states without public reporting.⁴⁰ The differences in the use of PCI were greatest for patients with cardiogenic shock. Interestingly, the mortality rate

High-risk findings on noninvasive study						CCS Class III or IV angina					
Symptoms: medical Rx						Stress test: med Rx					
Class III or IV: max Rx	A	A	A	A	A	High risk: max Rx	A	A	A	A	A
Class I or II: max Rx	A	A	A	A	A	High risk: no or min Rx	A	A	A	A	A
Asymptomatic: max Rx	U	A	A	A	A	Int risk: max Rx	A	A	A	A	A
Class III or IV: no or min Rx	A	A	A	A	A	Int risk: no or min Rx	U	U	A	A	A
Class I or II: no or min Rx	U	A	A	A	A	Low risk: max Rx	U	A	A	A	A
Asymptomatic: no or min Rx	U	U	A	A	A	Low risk: no or min Rx	I	U	A	A	A
Coronary anatomy	CTO of 1 vz; no other disease	1-2 vz disease; no prox LAD	1-vz disease of prox LAD	2-vz disease with prox LAD	3-vz disease; no left main	Coronary anatomy	CTO of 1 vz; no other disease	1-2 vz disease; no prox LAD	1-vz disease of prox LAD	2-vz disease with prox LAD	3-vz disease; no left main

B

FIGURE 2.13, Cont'd

TABLE 2.1 The ACC/AHA/SCAI/AMA-Convened PCIP/NCQA 2013 Performance Measure for Adults Undergoing Percutaneous Coronary Intervention

1. Comprehensive documentation of indications for PCI
2. Appropriate indication for elective PCI
3. Assessment of candidacy for dual antiplatelet therapy
4. Use of embolic protection devices in the treatment of patients with saphenous vein bypass graft disease
5. Documentation of preprocedural GFR and contrast dose used during the procedure
6. Radiation dose documentation
7. Postprocedural optimal medical therapy composite
8. Cardiac rehabilitation patient referral
9. Regional or national PCI registry participation
10. Annual operator and hospital PCI volume

ACC, American College of Cardiology; AHA, American Heart Association; AMA, American Medical Association; GFR, glomerular filtration rate; NCQA, National Committee for Quality Assurance; PCI, percutaneous coronary intervention; PCIP, Primary Care Information Project; SCAI, Society for Cardiovascular Angiography and Interventions. Reprinted with permission from Nallamothu BK, Tommaso CL, Anderson HV, et al. ACC/AHA/SCAI/AMA-Convened PCIP/NCQA 2013 performance measures for adults undergoing percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association task force on performance measures, the Society for Cardiovascular Angiography and Interventions, the American Medical Association-Convened Physician Consortium for Performance Improvement, and the National Committee for Quality Assurance. *Circulation*. 2014;29(8):926-949.

was not different among the states with and without public reporting. Other studies have suggested a positive impact of public reporting with a reduction in mortality rate.⁴¹ The decline in mortality rate in these studies may have been caused by improved selection of patients with a decision not to intervene in patients in whom the procedure was futile, but other factors could have contributed as well, including underreporting because of exclusions.⁴² Future studies are needed to determine the value of public reporting.

PUTTING GUIDELINES INTO PRACTICE

Guidelines have provided authoritative recommendations for the treatment of patients with cardiovascular disease.

The documents are lengthy and difficult to read and integrate into clinical practice. A number of efforts have been introduced to more effectively put guidelines into practice. These have included the AHA Get-with-the-Guidelines. This is a voluntary hospital program to record the following information on a simple web-based form at the time of discharge: patient demographics, hospital course, and the use of secondary prevention guidelines for ACSs, stroke, resuscitation, atrial fibrillation, and heart failure. In the participating hospitals, improvement in adherence to performance measures has been shown, and better short-term outcomes have been reported in all of these conditions.^{9,43,44} The limitation of this approach is that guidelines, particularly performance measures, do not deal with areas of the greatest uncertainty, fail to account for variations in local practice, do not account for comorbidities, and do

not have a process for continuous quality improvement based on outcomes.

A novel approach to overcome these limitations has been the introduction of the standardized clinical assessment and management plan (SCAMP).^{45,46} The goal is to improve quality by narrowing practice variability while providing continuous improvement of the critical pathways. Because of improved use of testing and treatment, SCAMPs also reduce cost as well. The process begins by identifying areas where there is significant practice variability because of uncertainty and lack of adequate data. A group of clinicians formulate a care pathway based on guidelines and expert opinion. Areas of knowledge gaps are clearly identified, and data that need to be collected to understand these gaps and variations in practice patterns are identified. The individual SCAMPs are intended to be brief and focused. The key component is that variations in practice are not prevented or discouraged but rather encouraged. When there is a deviation from the care pathway, the physician is prompted to document the rationale. Data are collected on specialized forms and entered into a database. After a set time period, which is typically 6 to 12 months, the SCAMP data are analyzed, focusing on the initial areas of uncertainty and practice variations. The committee then revises the SCAMPs based on the outcomes and pays particular attention to the outliers who did not follow the pathway. This results in a continuously updated pathway based on new knowledge and experience that is specific to the institution and practice. Initial experience with 49 SCAMPs in nine states has shown a decrease in practice variation, reduction in the unnecessary use of resources with reduced cost, and improvement in stakeholders' engagement.^{45,46}

CONCLUSIONS

The improvement in the quality of care is a fundamental goal for all aspects of medical care. The development of guidelines has been the cornerstone of this effort. Despite their recognized limitations, they provide valuable guidance for clinical practice and are the basis for all the other methods to improve quality. Appropriateness criteria are most germane to interventional cardiology because they are best applied to procedures and are likely to help reduce variability and improve quality. Performance measures, P4P, and public reporting may also be helpful, but further study is needed. Iterative clinical pathways such as SCAMPs need further study but provide some advantages over other methods by assessing variability in practice and focusing on areas of greatest uncertainty.

REFERENCES

- Geoffrey M. *Crossing the Quality Chasm*. Institute of Medicine; 2001.
- Califf RM. The benefits of moving quality to a national level. *Am Heart J*. 2008;156:1019-1022.
- Gibbons RJ, Smith S, Antman E. American College of Cardiology/American Heart Association clinical practice guidelines: part I: where do they come from? *Circulation*. 2003;107:2979-2986.
- Gibbons RJ, Smith SC Jr, Antman E. American College of Cardiology/American Heart Association clinical practice guidelines: part II: evolutionary changes in a continuous quality improvement project. *Circulation*. 2003;107:3101-3107.
- Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. 2013;127:268-310.
- Tricoci P, Allen JM, Kramer JM, et al. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA*. 2009;301:831-841.
- Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(2):e21-e129.
- Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87-165.
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. 2013;127:e362-e425.
- Jacobs AK, Ali MJ, Best PJ, et al. Systems of care for ST-segment-elevation myocardial infarction: a policy statement from the American Heart Association. *Circulation*. 2021;144(20):e310-e327.
- Menees DS, Gurm HS. Door-to-balloon time and mortality. *N Engl J Med*. 2014;370:181-182.
- Bradley EH, Herrin J, Wang Y, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med*. 2006;355:2308-2320.
- Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358:2218-2230.
- De Luca G, Navarese EP, Suryapranata H. A meta-analytic overview of thrombectomy during primary angioplasty. *Int J Cardiol*. 2013;166:606-612.
- Frobert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;369:1587-1597.
- Sabate M, Cequier A, Iniguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (examination): 1 year results of a randomised controlled trial. *Lancet*. 2012;380:1482-1490.
- Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons; endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation*. 2007;116:e148-e304.
- Anderson JL, Adams CD, Antman EM, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. 2011;123:e426-e579.
- Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. 2012;126:875-910.
- Gulati M, Levy PD, Mukherjee D, et al. AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;144(22):e368-e454.
- Lindner G, Pfortmueller CA, Braun CT, et al. Non-acute myocardial infarction-related causes of elevated high-sensitive troponin T in the emergency room: a cross-sectional analysis. *Intern Emerg Med*. 2014;9(3):335-339.
- Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med*. 2009;360:2165-2175.
- Farkouh ME, Domanski M, Fuster V. Revascularization strategies in patients with diabetes. *N Engl J Med*. 2013;368:1455-1456.
- Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on the management of patients with chronic stable angina). *Circulation*. 2003;107:149-158.
- Fraker TD Jr, Fihn SD, Gibbons RJ, et al. 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association task force on practice guidelines writing group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. *Circulation*. 2007;116:2762-2772.
- Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:e354-e471.
- Hlatky MA, Boothroyd DB, Baker L, et al. Comparative effectiveness of multivessel coronary bypass surgery and multivessel percutaneous coronary intervention: a cohort study. *Ann Intern Med*. 2013;158:727-734.



28. Kappetein AP, Head SJ, Morice MC, et al. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the syntax trial. *Eur J Cardiothorac Surg*. 2013;43:1006-1013.
29. Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report of the American College of Cardiology Foundation appropriateness criteria task force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation*. 2009;119:1330-1352.
30. Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation appropriate use criteria task force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol*. 2012;59:857-881.
31. Chan PS, Patel MR, Klein LW, et al. Appropriateness of percutaneous coronary intervention. *JAMA*. 2011;306:53-61.
32. Hannan EL, Samadashvili Z, Cozzens K, et al. Appropriateness of diagnostic catheterization for suspected coronary artery disease in New York State. *Circ Cardiovasc Interv*. 2014;7(1):19-27.
33. Marso SP, Teirstein PS, Kereiakes DJ, et al. Percutaneous coronary intervention use in the United States: defining measures of appropriateness. *JACC Cardiovasc Interv*. 2012;5:229-235.
34. Faxon DP. Assessing appropriateness of coronary angiography: another step in improving quality. *Ann Intern Med*. 2008;149:276-278.
35. Hemingway H, Chen R, Junghans C, et al. Appropriateness criteria for coronary angiography in angina: reliability and validity. *Ann Intern Med*. 2008;149:221-231.
36. Bonow RO, Masoudi FA, Rumsfeld JS, et al. ACC/AHA classification of care metrics: performance measures and quality metrics: a report of the American College of Cardiology/American Heart Association task force on performance measures. *Circulation*. 2008;118:2662-2666.
37. Nallamothu BK, Tommaso CL, Anderson HV, et al. ACC/AHA/SCAI/AMA-Convended PCIP/NCQA 2013 performance measures for adults undergoing percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association task force on performance measures, the Society for Cardiovascular Angiography and Interventions, the American Medical Association-Convended Physician Consortium for Performance Improvement, and the National Committee for Quality Assurance. *Circulation*. 2014;29(8):926-949.
38. Eijkenaar F, Emmert M, Scheppach M, et al. Effects of pay for performance in health care: a systematic review of systematic reviews. *Health Policy (New York)*. 2013;110:115-130.
39. Resnic FS, Welt FG. The public health hazards of risk avoidance associated with public reporting of risk-adjusted outcomes in coronary intervention. *J Am Coll Cardiol*. 2009;53:825-830.
40. Joynt KE, Blumenthal DM, Orav EJ, et al. Association of Public Reporting for Percutaneous Coronary Intervention with utilization and outcomes among Medicare beneficiaries with acute myocardial infarction. *JAMA*. 2012;308:1460-1468.
41. McCrum ML, Joynt KE, Orav EJ, et al. Mortality for publicly reported conditions and overall hospital mortality rates. *JAMA Intern Med*. 2013;173:1351-1357.
42. McCabe JM, Joynt KE, Welt FG, et al. Impact of public reporting and outlier status identification on percutaneous coronary intervention case selection in Massachusetts. *JACC Cardiovasc Interv*. 2013;6:625-630.
43. Tam LM, Fonarow GC, Bhatt DL, et al. Achievement of guideline-concordant care and in-hospital outcomes in patients with coronary artery disease in teaching and nonteaching hospitals: results from the Get with the Guidelines—coronary artery disease program. *Circ Cardiovasc Qual Outcomes*. 2013;6:58-65.
44. Somma KA, Bhatt DL, Fonarow GC, et al. Guideline adherence after ST-segment elevation versus non-ST segment elevation myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2012;5:654-661.
45. Rathod RH, Farias M, Friedman KG, et al. A novel approach to gathering and acting on relevant clinical information: SCAMPs. *Congenit Heart Dis*. 2010;5:343-353.
46. Farias M, Jenkins K, Lock J, et al. Standardized clinical assessment and management plans (SCAMPs) provide a better alternative to clinical practice guidelines. *Health Aff (Millwood)*. 2013;32:911-920.



3 Vascular Access And Closure

SRIPAL BANGALORE

FEMORAL ARTERIAL ACCESS, 23

Introduction, 23
Anatomic Considerations, 23
Preprocedural Considerations, 24
Procedure, 25
Special Considerations, 26
Postprocedure Care, 28
Complications, 28

FEMORAL ARTERIAL ACCESS SITE CLOSURE, 33

Introduction, 33
Manual Compression, 33
Mechanical Compression, 33
Assisted Compression Devices and Topical Hemostasis Accelerators, 36

Vascular Closure Devices, 36

RADIAL ARTERIAL ACCESS AND CLOSURE, 44

Introduction, 44
Anatomic Considerations, 44
Preprocedural Considerations, 44
Procedural Considerations, 47
Closure and Postprocedural Care, 47
Complications and Challenges, 49

ULNAR ARTERIAL ACCESS AND CLOSURE, 52

DISTAL RADIAL ARTERIAL ACCESS AND CLOSURE, 53

BRACHIAL ARTERIAL ACCESS AND CLOSURE, 53

Introduction and Anatomy, 53

Procedure, 54
Closure and Complications, 54

VENOUS ACCESS AND CLOSURE, 54

Right Heart Catheterization via the Basilic Vein, 54
Other Venous Access—Femoral, Internal Jugular, and Brachial, 54

CONCLUSIONS, 54

Arterial access for common coronary and vascular procedures can be obtained via the common femoral artery, radial, distal radial, ulnar, or brachial arteries. More recently, the subclavian artery and direct aortic access are being used for transcatheter aortic valve replacement procedures. Arterial access site complications are common in interventional procedures,¹ and knowledge of the anatomy, optimal access techniques, and optimal techniques to obtain hemostasis postprocedure are critical to minimize such complications.

FEMORAL ARTERIAL ACCESS

Introduction

The common femoral artery (CFA) is the most commonly used site for percutaneous arterial access for coronary diagnostic, interventional, structural heart, and peripheral vascular procedures, although transradial access is on the rise in the United States and worldwide.² The femoral artery is often favored for its size, ease of insertion, and ability to provide a relatively less tortuous path to the heart.

Anatomic Considerations

The CFA is a continuation of the external iliac artery and passes through the femoral sheath and branches into the superficial femoral artery (SFA) and the profunda femoris artery (PFA) (Figure 3.1A). The femoral sheath has three compartments—from medial to lateral—the femoral canal, which contains the efferent lymphatic vessels and lymph node embedded in areolar tissue; the intermediate compartment, which contains the femoral vein; and the lateral compartment, which contains the femoral artery (Figure 3.1B). Lateral to the femoral artery and outside the femoral sheath is the femoral nerve. The relationship is important to avoid accidental puncture of the femoral vein or the femoral

nerve. The CFA in the femoral sheath is the ideal site for femoral artery cannulation because the artery is large, less tortuous, and less affected by atherosclerosis, and it sits against the femoral head, making it easier to palpate and also more compressible to achieve effective hemostasis. In addition, the femoral sheath provides effective scaffolding, thereby limiting the spread of hematoma, acting as a tamponade to the arteriotomy site, and preventing pseudoaneurysm formation.³

Knowledge of the anatomy of the CFA is essential not only to ensure sheath placement at the ideal site to avoid complications but also to troubleshoot difficulties while cannulating the artery. The access site complications are minimized if access is obtained at the “ideal” femoral puncture, which would avoid either a high puncture or a low puncture and also takes into consideration possible anatomic variations of femoral artery bifurcation. The inguinal ligament is usually 15 mm superior to the midfemoral head, and in the majority of cases (~77%), the bifurcation of the femoral artery is below the level of the femoral head.⁴ Hence, a “target zone” from the midfemoral head to the lower border of the femoral head is ideal (Figure 3.2, zone B). However, the “ideal” spot (even in the 23% of cases with high femoral artery bifurcation) is about 1 cm lateral to the most medial aspect of the femoral head, midway between its superior and inferior borders (*Rupp’s rule*) (Figures 3.2 and 3.3).⁴

A “low” cannulation into the SFA or the PFA increases the risk of ischemic complications because of the smaller size of these branch arteries; increases the risk of bleeding, hematoma, and pseudoaneurysm because of lack of an underlying compressible bony structure or the scaffolding effect of the femoral sheath resulting in ineffective hemostasis; and increases the risk of arteriovenous fistula (AVF) as the tributaries of the femoral vein overlie the SFA, increasing the risk of through-and-through puncture to access the artery.³ However, a “high” cannulation above

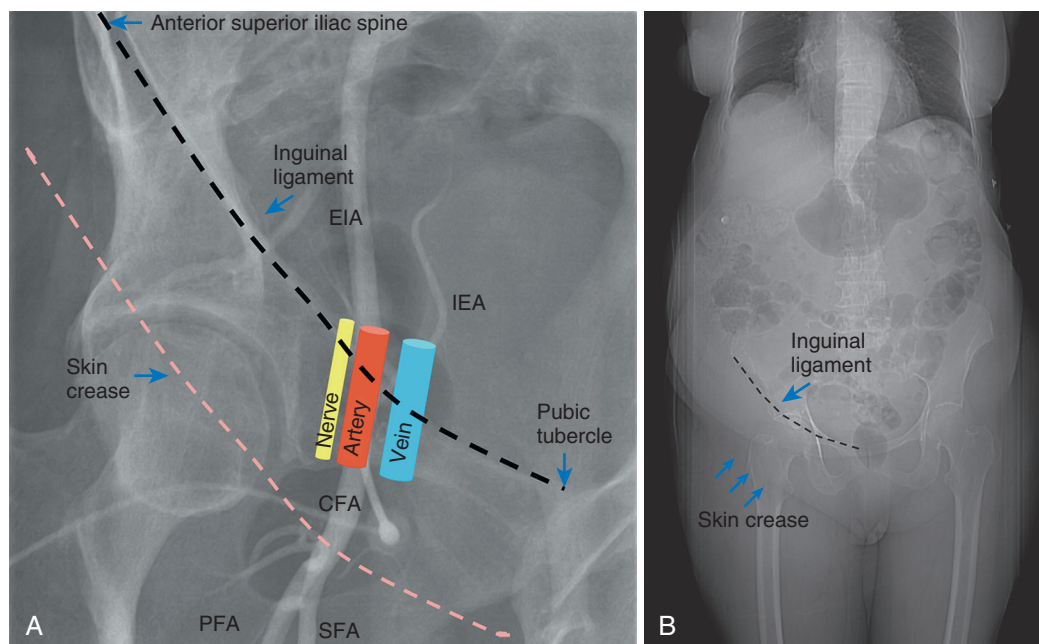


FIGURE 3.1 Femoral artery anatomy. **A**, Relationship of the femoral artery to other neurovascular bundles and the inguinal ligament. **B**, Variability in the relationship between skin crease and the inguinal ligament. CFA, Common femoral artery; EIA, external iliac artery; IEA, Inferior epigastric artery; PFA, profunda femoris artery; SFA, superficial femoral artery. (A, Adapted from Bangalore S, Bhatt DL. Femoral arterial access and closure. *Circulation*. 2011;124(5):e147-e156.)

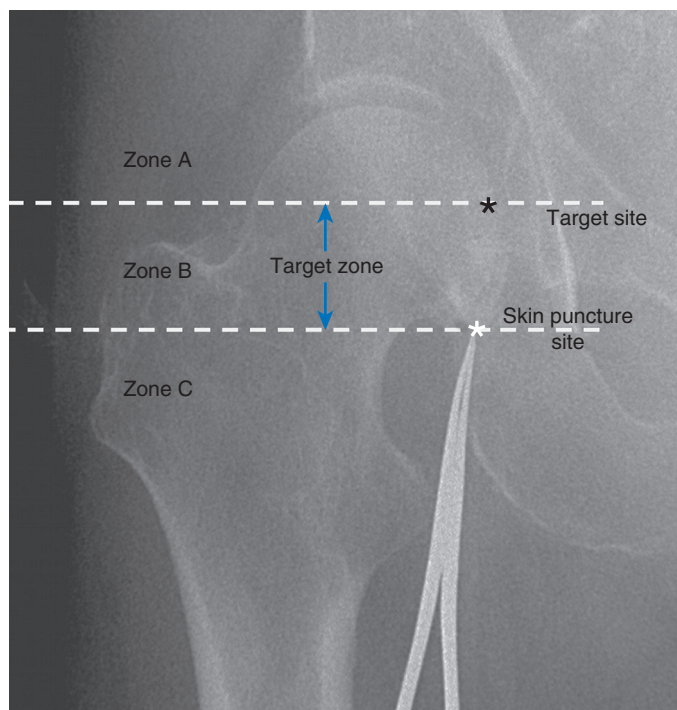


FIGURE 3.2 Target zone for femoral arterial access. The ideal skin puncture site (indicated by the hemostatic clamp and the white star) and the ideal arterial cannulation site (indicated by the black star) are shown.

the inguinal ligament (above the lower border of the inferior epigastric artery on the femoral angiogram) into the external iliac artery makes it harder to compress the artery because of a lack of underlying bony structure, which increases the risk of retroperitoneal bleeding.⁵ In addition, a “high” cannulation of the CFA underneath the inguinal ligament also prevents effective compression by the taut inguinal ligament, thereby increasing bleeding and hematoma.

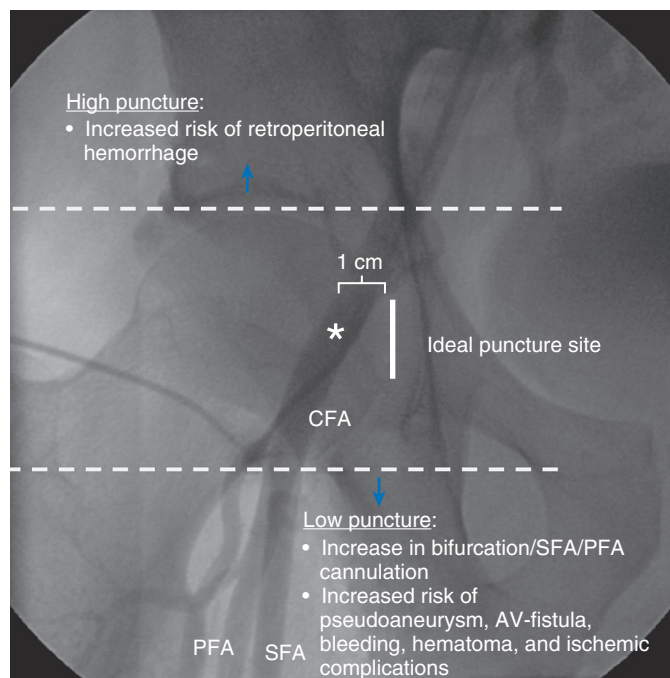


FIGURE 3.3 Rupp's rule/ The ideal arterial puncture site is a point 1 cm lateral to the medial-most point of the femoral head in an anteroposterior projection on fluoroscopy (indicated by the white star). AV, Arteriovenous; CFA, common femoral artery; PFA, profunda femoris artery; SFA, superficial femoral artery.

Preprocedural Considerations

A thorough history and physical examination before the procedure may reveal characteristics that indicate the femoral route is not an ideal access site for the patient. Clinically significant history, including the indications for the procedure, should be obtained and recorded in the patient's chart. Patients with severe peripheral vascular disease, especially with known severe disease of the CFA,

those with iliofemoral bypass grafts or stents, those with a superficial infection at the groin puncture site or morbid obesity, those with heart failure or low back pain who may not be able to lie supine for prolonged periods of time, those on anticoagulation or thrombolytic therapy, those with recent use of a collagen plug-based vascular closure device (VCD), and those with recent complications of the femoral artery (e.g., those with a pseudoaneurysm or AVF) may not be ideal candidates for femoral access and should be considered for alternatives, such as radial artery access. However, these conditions by themselves are not absolute contraindications for femoral access, and in many instances, the procedure can be performed using a small size sheath or in other cases by the use of the contralateral femoral artery. In addition to a routine physical examination, inspection of the groin for any signs of infection, palpation of the femoral and distal pulses (bilateral dorsalis pedis, posterior tibial, and popliteal arteries), and auscultation for bruits should be performed and documented in the patient's chart. In addition, a review of prior femoral angiograms, if available, can help plan the optimal location for an ideal femoral arterial puncture. The medications the patient is taking should be reviewed. In addition, laboratory evaluation should include measurement of hemoglobin, hematocrit, platelets, coagulation parameters, creatinine, and electrolytes.

Procedure

One or both of the groins should be prepped and draped in a sterile manner. Conscious sedation should be administered using a combination of sedative and analgesic based on local practice and taking into consideration patient age (reduced dose in older adults) and renal and hepatic functions. Conscious sedation ensures better patient cooperation during the procedure, although it can be performed using local anesthetic alone. The first step in establishing femoral access is to locate the skin site that corresponds to the "ideal" femoral puncture site. Various external landmarks have been used to access the femoral artery (Table 3.1),⁶ but the most popular one is by using fluoroscopic landmarks (see Figure 3.2). In the fluoroscopic technique, the femoral head is visualized under fluoroscopy in posteroanterior (PA) projection, and a metal clamp is then placed on the skin at the lower border of the femoral head. This corresponds to the skin puncture site, and a puncture at this site at a 30- to 45-degree angle will cannulate the femoral artery, corresponding to the middle of the femoral head, which is the ideal puncture site. The steps involved in femoral artery cannulation are outlined in Table 3.2. After a femoral sheath is inserted, the side port should be connected to the pressure transducer to obtain a femoral artery pressure waveform. Any dampening of the pressure waveform at this stage may indicate atherosclerosis in the CFA or the external iliac or sheath in a dissection plane. It is highly recommended to obtain a femoral angiogram (30- to 45-degree ipsilateral oblique view) prior to coronary angiography (unless the glomerular filtration rate is low) to ensure correct placement of the femoral sheath in the CFA and to detect any complications such as dissection, perforation, or even the presence of

TABLE 3.1 External Landmarks for Identifying the "Ideal" Femoral Artery Site

Skin or inguinal crease	Skin puncture site 2–3 cm below the midpoint of the skin crease. Disadvantage: Variability in the relationship between the inguinal ligament and skin crease, especially in morbidly obese patients, resulting in a lack of consistency in localization of the ideal puncture site (see Figure 3.1).
Bony landmarks	Skin puncture site 2–3 cm below the midinguinal point (midpoint between the anterior superior iliac spine and pubic tubercle). Disadvantage: Variability in the relationship between the inguinal ligament and the midinguinal point, resulting in a lack of consistency in localization of the ideal puncture site.
Maximal impulse	Skin puncture site at the site of maximal impulse. Disadvantage: Site of maximal pulsation may not correspond to the midfemoral site (ideal puncture site), especially in obese patients, resulting in low or high cannulation.
Fluoroscopic landmark	Skin puncture site at a point that corresponds to the lower border of femoral head on fluoroscopy. Provides the most consistent landmark to the midfemoral common femoral artery site.

TABLE 3.2 Steps in Femoral Arterial Cannulation

- Step 1: Administer adequate local anesthetic agent (10–20 cc) at the site of the skin entry site over the location of the femoral artery starting with a dermal bleb and working deeper. Anesthetize the area around the artery (above, medial, and lateral).
- Step 2*: Palpating the femoral artery with the index and middle finger of one hand, enter the skin at the lower border of head of the femur (identified on fluoroscopy) with an 18-gauge needle at a 30- to 45-degree angle using the modified Seldinger technique (anterior wall stick). Some operators use fluoroscopy at this stage to ensure that the needle is at the level of the midfemoral head.
- Step 3: After the femoral artery is cannulated with the needle, ensure pulsatile blood flow before advancing a 0.035-inch J-tipped guidewire into the femoral and iliac arteries and onto the descending aorta. If any resistance is encountered, advance the wire under fluoroscopy.
- Step 4: A small (2–3 mm) skin nick can be made at this stage (optional); exchange the cannulation needle to a femoral arterial sheath with the dilator inside it.
- Step 5: Remove the J-tipped guidewire and the dilator and flush the side port of the sheath using heparinized saline.
- Step 6: Perform femoral angiography in the ipsilateral anterior oblique view at a 30- to 45-degree angulation to visualize the sheath insertion site in relation to the common femoral artery bifurcation. Consider repeat femoral angiography in the posteroanterior projection if the cannulation appears too high on the ipsilateral anterior oblique view. Some operators prefer to leave the J-tipped guidewire in before femoral angiography to avoid injecting into the vessel wall, thereby increasing the risk of dissection.

*Some operators use the nick and tunnel approach at this stage, in which a small nick (2–3 mm) is made parallel to the skin crease and an artery forceps is used to create a tunnel. Advantage: Bleeding will manifest as oozing rather than a hematoma. Disadvantage: Need for a separate nick and tunnel if the femoral artery cannulation cannot be obtained at the site of the skin nick.

severe atherosclerotic disease in the CFA. The ipsilateral oblique view should not be used to determine a "high puncture." If a high puncture is suspected based on the ipsilateral oblique view, repeating the femoral angiogram in the PA or the contralateral oblique view may be helpful to confirm the puncture site. Detection of problems at this stage will help plan subsequent procedures before any anticoagulation is administered (deferral of percutaneous coronary intervention [PCI] for high stick or any perforation or dissection) and considerations for access site



management at the end of the procedure (manual compression vs VCD). In addition, flushing the sheath between each catheter exchange can prevent the formation of a clot within the sheath.

Special Considerations

Using a Micropuncture Needle

The standard Seldinger needle used for the femoral artery cannulation is an 18-gauge needle. A micropuncture needle is a 21-gauge needle, which decreases the size of the hole by 56% and the flow through the hole by nearly sixfold over a standard 18-gauge needle, potentially decreasing complications from errant sticks or inadvertent back wall punctures.⁷ However, there are no robust data to support the routine use of micropuncture in all cases to reduce the risk of femoral access site complications. For access using a micropuncture needle, the skin is entered at the site corresponding to the lower border of the femoral head on fluoroscopy using the 21-gauge needle. Some operators use fluoroscopy before entering the vessel to ensure that the tip of the needle is at the desired site and repositioning as needed. After ensuring blood flow from the hub (may not be as pulsatile), a floppy-tipped 0.018-inch guidewire is then advanced into the CFA and the external iliac artery. Advancing the guidewire under fluoroscopy may be preferred because resistance to advancement is better seen than felt with the finer guidewire of the micropuncture set. The needle is now exchanged for a 4-Fr short catheter with a 3-Fr inner dilator. Both the guidewire and the dilator are removed, at which point there should be pulsatile blood flow, followed by introduction of the 0.035- or 0.038-inch guidewire and exchange of the 4-Fr catheter to the appropriately size femoral sheath. Alternatively, the inner dilator can be used to perform femoral angiography. If the cannulation site is too high or low, the dilator is removed, and pressure is applied to ensure hemostasis and reaccess are performed at the optimal location.

Using a SmartNeedle Percutaneous Doppler Vascular Access Device

In patients with difficult-to-palpate femoral pulses, the SmartNeedle (Vascular Solutions) may be helpful. The SmartNeedle consists of a detachable Doppler probe inside the lumen of a standard introducer needle. This is connected to a handheld monitor by a cable, and the flow is detected by an audio output. Attach the cable of the needle to the connector on the SmartNeedle monitor, turn on the monitor, and adjust the volume as needed. Test the system by dipping the needle in water and moving it back and forth. An audible Doppler signal should be heard. Flush the needle with saline to remove any air. Now insert the needle through the skin with a saline syringe connected while listening to the Doppler signal. Express a small amount of saline through the tip to clear any air bubbles. Move the needle in a circular motion while listening to the Doppler flow signal. As the needle approaches the artery, the Doppler signal becomes louder and pulsatile, thus assisting femoral arterial cannulation. Whereas arterial flow may be identified as a pulsatile high-frequency sound, venous flow is a low-frequency sound. Care must be

taken not to palpate the artery or vein while advancing the needle because this can compress the vein and obliterate the venous signal. When a Doppler signal is detected, the area should be scanned for the loudest signal and then the needle further advanced in the direction. When the needle enters the artery, there is a pulsatile flow of blood (may not be as brisk as a regular needle because of the probe being in place). The Doppler probe is now removed from the needle, a guidewire is inserted, and the other steps are similar to what is described in [Table 3.2](#). Compared with a standard needle, the SmartNeedle has been shown to result in a greater proportion of successful femoral arterial cannulations on first attempt and to reduce the risk of hematoma.⁸

Using Ultrasound Guidance

For patients with a difficult-to-palpate femoral artery pulse, femoral artery cannulation under ultrasound guidance is an option. Arterial cannulation under ultrasound guidance is similar to central venous access using a similar approach. The advantage of this approach is direct visualization of the artery before cannulation, thereby avoiding cannulation into diseased segments, cannulating branch arteries when there are anatomic variants (high bifurcation) or accidental venous puncture in anatomical variants where the femoral vein (or its tributaries) lies directly above the artery. The disadvantages are the need for a vascular transducer probe and extra time to set up the equipment and for the additional steps involved. The technique involves using a 7-MHz vascular transducer probe draped in a sterile sleeve. The ultrasound is then held at the site of the proposed skin puncture site (determined on fluoroscopy) and moved caudally to visualize the femoral bifurcation and then cranially ([Figure 3.4](#)). The femoral artery can be differentiated from the femoral vein because it is less compressible, by the direction of blood flow on color Doppler ultrasonography, and by a triphasic signal (vs a more monophasic signal for the femoral vein) on pulse Doppler ultrasonography ([Figure 3.5](#)). When a relatively disease-free segment is identified in the CFA, arterial cannulation can be performed under direct ultrasound guidance by holding the ultrasound probe in one hand or by a second operator and the needle in the other hand. Local anesthesia is administered around the artery under direct ultrasound guidance. The Seldinger needle is then used and its position adjusted based on the ultrasound image until the artery is cannulated and confirmed by pulsatile blood. An ultrasound probe with an integral needle guide and built-in needle position sensors are now available (see [Figure 3.4](#)). Together these project on the ultrasound monitor an enhanced virtual image of the needle as it moves through the tissue toward and into the target vessel. After the path is confirmed on the monitor, the needle is inserted through the needle guide while advancing the needle under direct ultrasound visualization and confirmed by pulsatile blood (see [Figure 3.4](#)). The guidewire is then inserted and the needle exchanged for an appropriately size femoral artery sheath as described previously.

Ultrasound-guided femoral arterial cannulation has been shown to aid vascular access in patients with an absent

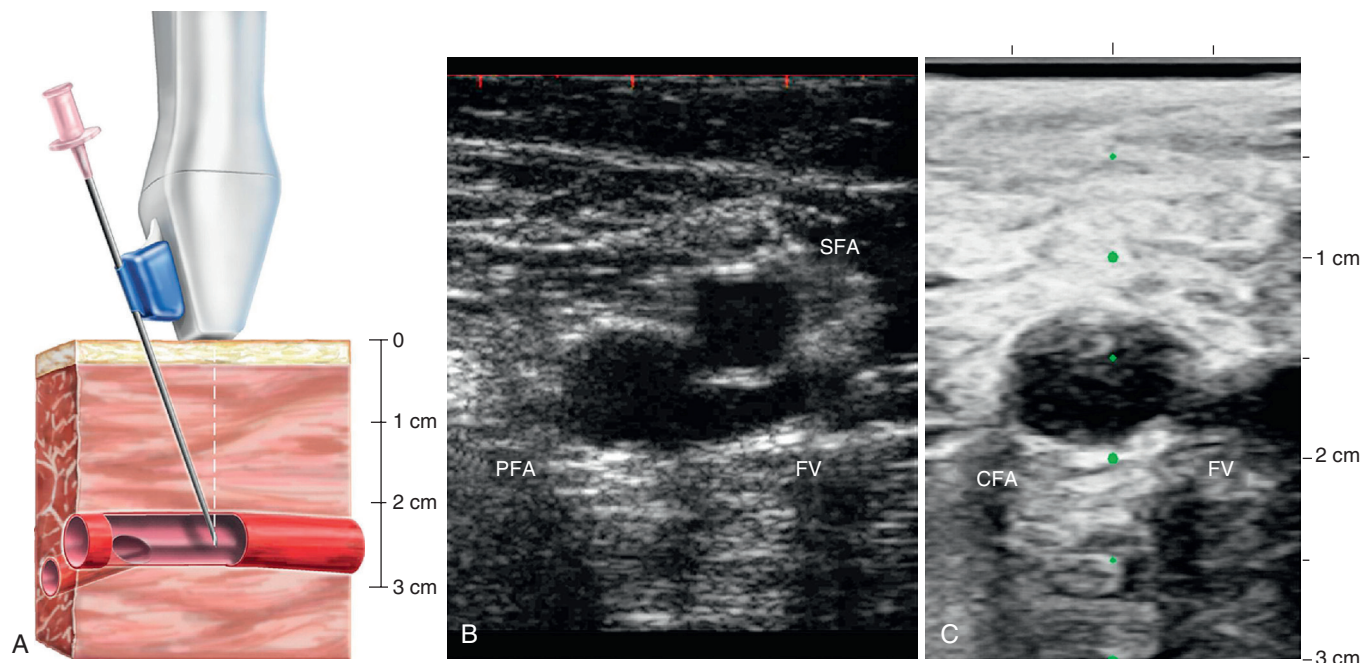


FIGURE 3.4 Ultrasound-guided femoral arterial cannulation. **A**, Ultrasound probe with the needle guide. The attached needle guide fixes the needle's angle of entry to intersect the vessel at the imaging plane 1.5 cm, 2.5 cm, or 3.5 cm below the skin, depending on the needle guide chosen. **B**, Axial view of the femoral artery bifurcation, identifying the separation of the profunda femoral artery (PFA) and superficial femoral artery (SFA). The femoral vein (FV) is differentiated from the arteries using compression. **C**, The probe is moved superiorly until the common femoral artery (CFA) is visualized. During needle advancement, the anterior wall of the vessel is kept under the central target line (green circles), which indicates the path of the needle. (Reproduced with permission from Seto AH, Abu-Fadel MS, Sparling JM, et al. Real-time ultrasound guidance facilitates femoral arterial access and reduces vascular complications: FAUST (Femoral Arterial Access With Ultrasound Trial). *JACC Cardiovasc Interv.* 2010;3(7):751-758.)

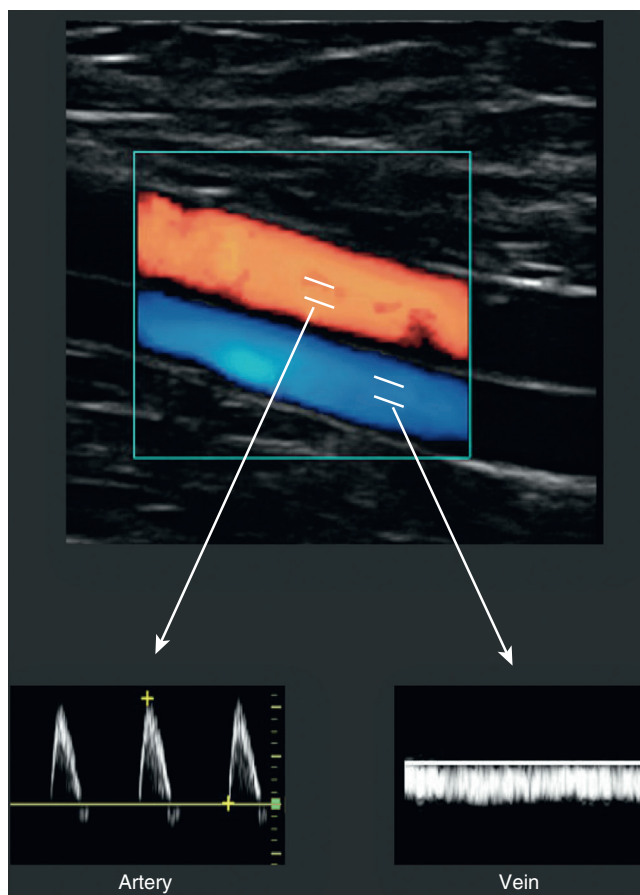


FIGURE 3.5 Color and pulse Doppler ultrasound to differentiate the artery from a vein. (Adapted from Bangalore S, Bhatt DL. Femoral arterial access and closure. *Circulation.* 2011;124(5):e147-e156.)

palpable pulse or after unsuccessful palpation-guided cannulation.⁹ In a meta-analysis of seven randomized controlled trials with 3180 patients randomized to standard access versus ultrasound-guided femoral access, ultrasound-guided femoral access resulted in a higher first attempt success rate (82.0% vs 58.7%; $P < .0001$), reduced time to access, number of attempts, vascular complications (1.3% vs 3.0%; $P = .02$), access site hematoma (1.2% vs 3.3%; $P = .01$), and venipuncture (3.6% vs 12.1%; $P < .00001$). However, there were nonsignificant differences in major bleeding (0.7% vs 1.4%; $P = .19$).¹⁰ As such, ultrasound-guided access should be considered when possible in most patients.¹¹

Femoral Arterial Cannulation in Challenging Patient Subgroups

Morbidly Obese Patients

Femoral arterial cannulation in morbidly obese patients can be a challenge because the artery may be difficult to palpate, the skin at the ideal puncture site may be excoriated, and the folds of adipose tissue may make femoral access a challenge. Considerations should be given to alternatives such as radial access. However, femoral arterial cannulation using a SmartNeedle (Teleflex) or under the guidance of ultrasound and using a micropuncture needle can be particularly helpful. Care must be taken to advance the needle at an angle more than the usual 30 to 45 degrees to avoid a high cannulation. In addition, with the needle in the subcutaneous tissue and before puncturing the artery, it may be helpful to use fluoroscopy to ensure proper positioning of the needle. In addition, a long guidewire with extra support (like an amplatz stiff wire) should preferably be used when exchanging the needle for a femoral artery



sheath, and consideration should be given to using a longer femoral artery sheath to ensure that it is well within the artery.

Patients with Iliofemoral Bypass Grafts

In patients with iliofemoral bypass grafts, consideration should be given to alternatives such as radial access or use of the nongrafted side (if available). If femoral access is desirable, consideration should be given to micropuncture with the intention of aiming for the hub of the graft. The micropuncture guidewire should be advanced under fluoroscopy, and if resistance is encountered, angiography either through the micropuncture needle or after exchanging the needle for a 3-Fr micropuncture dilator should be considered to roadmap the graft. After a roadmap is established, either the native artery (if patent) or the graft should be wired.

Patients with Calcified Femoral Artery

In some patients, the femoral artery calcification is visible on fluoroscopy and can potentially outline the artery and serve as a roadmap of the artery. In such cases, femoral artery cannulation can be performed under direct fluoroscopic guidance, aiming the needle (preferably a micropuncture needle) at the CFA at the center of the femoral head. However, consideration should be given to the fact that the artery could have severe atherosclerotic disease, making closure a challenge and increasing the risk of ischemic limb complications. In addition, heavily calcified arteries are less compressible and hence more prone to bleeding. Consideration should therefore be given for an alternative route such as radial access.

Postprocedure Care

The risk of complication with femoral arterial access is directly related to the size of the sheath, and consideration should be given to use the smallest size sheath when possible.¹² In addition, the sheath should be left in the artery for the shortest duration required. The sheath should be removed and hemostasis obtained either by manual compression or by using a VCD as described in the next section. Using the sheath for prolonged periods of time for arterial line access should be avoided, especially for sheaths larger than 4 Fr, and consideration should be given to obtaining a radial arterial line for longer term use. Patients should be advised to remain on bed rest and closely monitored during the initial postprocedural period. The duration of the bed rest period depends on the site and size of the vascular access, the means by which hemostasis was achieved, puncture-site stability, and the patient's medical conditions. The access site and distal pulsations should be periodically monitored. In addition, urinary output, cardiac symptoms, pain, other indicators of systemic complications, and vital signs should be monitored and recorded in the chart. After the period of bed rest, the initial ambulation of the patient must be supervised, and the patient should be closely monitored for bleeding.

Complications

The femoral access site is a frequent source of complications. The rate of complication varies between less than

1% and greater than 20%, depending on the patient population studied, the type of complication, and the definition used. However, there has been a significant decline in the complication rates in the contemporary era despite performance of PCI in older patients and the use of more potent antiplatelet and antithrombotic agents.^{13,14} Femoral access site complications prolong the hospital stay and are associated with a significant increase in cardiovascular events, including death.^{15,16} Femoral access site complication is dependent on several patient- and procedure-specific factors. Patient-specific risk factors include older age, female gender, lower body mass index, hypertension, peripheral vascular disease, known bleeding diathesis, severe renal impairment, being on anticoagulation before and after the procedure, peak activated clotting time, and procedure duration.^{13,16-19} Procedure-specific risk factors include the use of a larger sheath size (>6 Fr),^{13,20} the location of the femoral puncture site,²¹ and the use of glycoprotein (GP) IIb/IIIa inhibitors.²²

Bleeding and Hematoma

The femoral arterial access site is a frequent source of bleeding and hematoma. The incidence is around 0.8% to 23% and is the most common access site-related complication.^{13,23,24} Patients experiencing major femoral bleeding have a significantly longer postprocedure hospital stay and excess morbidity and mortality in the first 30 days compared with patients without major femoral bleeding.^{13,16,19} Contributing factors include a low or high femoral puncture, ineffective manual compression, a back wall femoral arterial wall puncture, accidental puncture of the vein, and the use of GP IIb/IIIa inhibitors.²² A hematoma usually presents as swelling surrounding the puncture site, which is often painful and results in difficulty moving the leg or skin discoloration. The presentation depends on the size of the hematoma (small <1 cm; medium, 1–5 cm; large >5 cm) and the acuity. A large hematoma can present with signs of hemodynamic instability with tachycardia, hypotension, or both. Some patients may present with a vasovagal reaction with bradycardia and hypotension caused by severe pain and compression of the underlying artery. Treatment includes manual compression at the site of the hematoma, fluid resuscitation or blood transfusion as needed for hemodynamic instability, prolonged bed rest, and interruption or reversal of anticoagulation or antiplatelet agents if necessary. Close monitoring for recurrence by outlining the hematoma and frequent measurement of the girth of the thigh and serial complete blood cell count is important to detect any further bleeding. Rarely, surgical evacuation of the hematoma may be required. Many hematomas resolve within a few weeks; however, care must be taken to prevent infection at the site of the hematoma.

Retroperitoneal Hemorrhage

Retroperitoneal hemorrhage, bleeding that occurs behind the serous membrane lining (peritoneum,) the walls of the abdomen and pelvis, is usually caused by a high femoral puncture above the inguinal ligament (lower margin of the inferior epigastric artery on fluoroscopy) or a posterior wall puncture. The incidence is around 0.1% to 0.4%, and it can be fatal if not recognized early.^{13,14,23,24} Risk factors



FIGURE 3.6 Cullen's sign (A) and Grey Turner's sign (B). (Reproduced with permission from Chauhan S, Gupta M, Sachdev A, D'Cruz S, Kaur I. Cullen's and Turner's sign associated with portal hypertension. *Lancet*. 2008;372(9632):54.)

include female gender, low body surface area, high arterial puncture, GP IIb/IIIa use, and chronic renal insufficiency.^{25,26} Patients usually present with ipsilateral flank or lower back pain, vague abdominal pain, and symptoms and signs of hypotension. Physical examination may show tachycardia and hypotension with Grey Turner's (bruising or blue discoloration of the flanks) or Cullen's (bruising or blue discoloration around the umbilicus) sign (Figure 3.6). Often there is no hematoma at the site of the femoral puncture site, and the only manifestation may be tachycardia and hypotension; therefore, a high clinical suspicion is required for early diagnosis. Diagnosis can be confirmed by computed tomography (CT) of the pelvis without contrast (Figure 3.7) or on femoral angiography showing frank extravasation of contrast into the pelvis (Figure 3.8). Treatment includes fluid resuscitation or blood transfusion as needed for hemodynamic instability, prolonged bed rest, and interruption of anticoagulation if necessary. Serial monitoring of blood pressure and a complete blood count should be performed. Definitive treatment for ongoing hemorrhage includes surgical evacuation of the hematoma with local repair of the artery or contralateral femoral arterial access with balloon tamponade at the site of perforation. In most cases, prolonged balloon tamponade will effectively seal the leakage, but in some cases, a covered stent may be required.

Arteriovenous Fistula

The incidence of AVF (Figure 3.9A) formation after femoral artery cannulation is low (<0.2%).^{14,23,24} The risk factors for AVF include a low or high femoral puncture, multiple

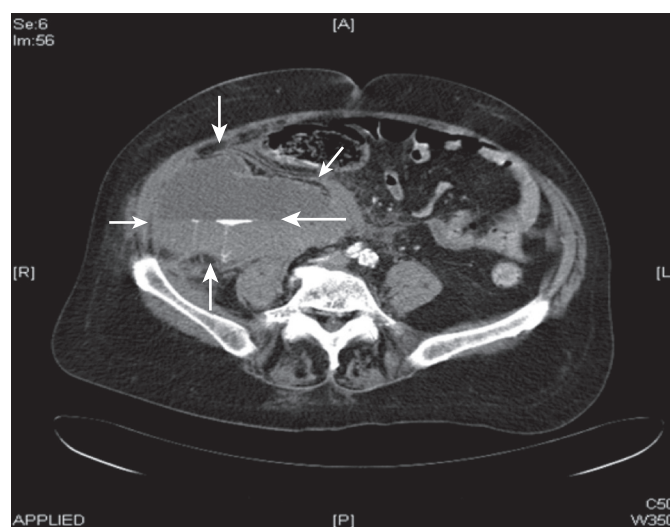


FIGURE 3.7 Abdominal computed tomography with contrast demonstrating a large retroperitoneal hemorrhage (arrows) with fluid level. (Modified with permission [open access journal] from Heuer M, Kaiser GM, Moeninghoff C, Paul A. Retroperitoneal hematoma: Vascular complication after percutaneous coronary intervention. *Int J Case Rep Images*. 2010;1(3):15-16.)

access attempts, puncture of the overlying femoral vein or its tributaries, and ineffective manual compression. Patients may be asymptomatic or present with pain and swelling at the groin site. Rarely, patients present with symptoms and signs of increased cardiac output or limb ischemia (intermittent claudication, ulcer) or deep vein thrombosis. On physical examination, a bruit may be

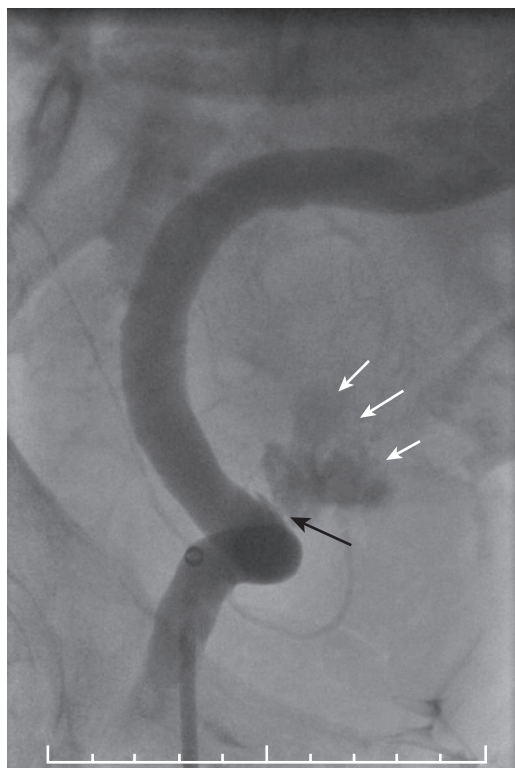


FIGURE 3.8 Retroperitoneal hemorrhage. Femoral angiogram showing a tortuous external iliac artery and contrast extravasation into the pelvis (white arrows). The site of perforation is indicated by the black arrow. Attempt at hemostasis using a covered stent failed, and the artery was repaired and hemostasis obtained by surgery. (Image courtesy of Drs. Ivan Pena Singh and Sohah Iqbal, New York University School of Medicine, New York.)

heard on auscultation and a thrill felt on palpation. Diagnosis is by color Doppler ultrasonography and rarely angiography (see Figure 3.9A) or CT (Figure 3.9B) is needed. For small AVFs and in asymptomatic patients, the treatment is observation and serial ultrasound examination. Most resolve with time. For large AVFs, ultrasound-guided compression is the treatment of choice. Other options include use of a balloon tamponade, covered stent, endovascular coils, and if all else fails, surgical repair.

Pseudoaneurysm

A pseudoaneurysm is defined as an arterial rupture of one or more layers of its walls, contained by overlying fibromuscular tissue, which communicates with an artery by a neck or sinus tract. The incidence of pseudoaneurysm is 0.3% to 9.0%.^{14,23,24} Risk factors for pseudoaneurysm include a low femoral puncture site and ineffective manual compression after sheath removal. The patient usually presents with swelling or pain or a large hematoma at the site. A large pseudoaneurysm can present with symptoms of nerve compression (limb weakness and paresthesia). A pseudoaneurysm can rupture, causing abrupt swelling and severe pain. A physical examination may reveal a pulsatile mass with a bruit, thrill, or both. The diagnosis is made on color Doppler ultrasonography (Figure 3.10A). It can also be diagnosed by angiography or CT (Figure 3.11). Treatment depends on the size of the pseudoaneurysm. A small pseudoaneurysm (≤ 2 cm) usually resolves spontaneously

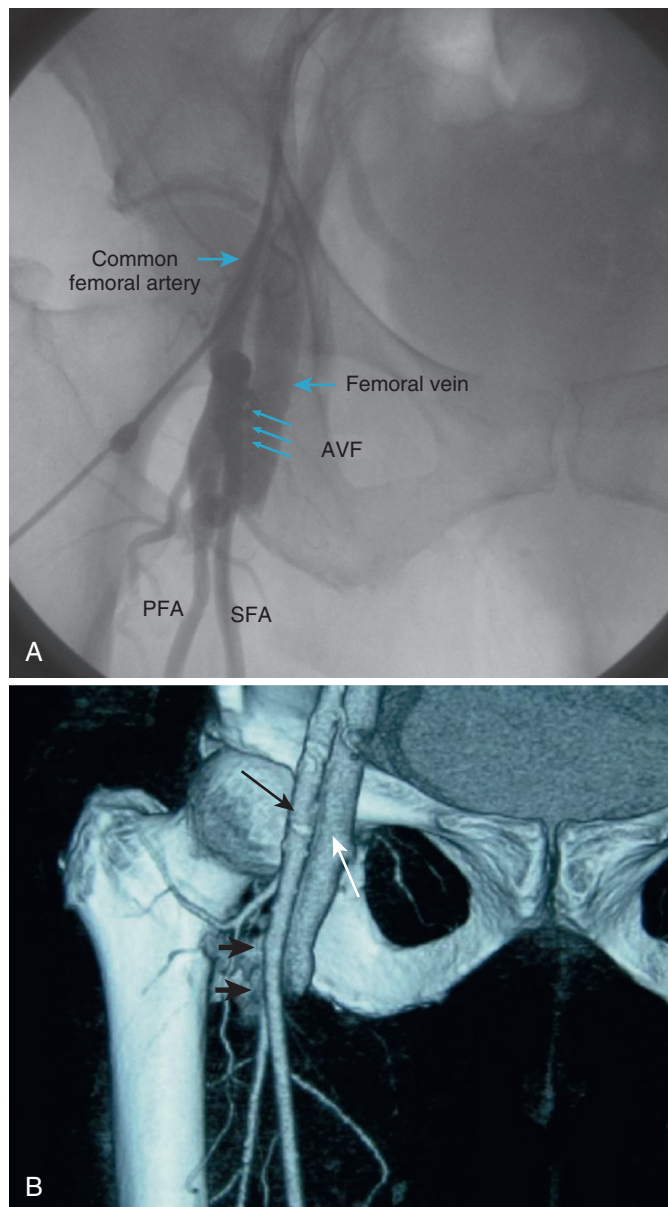


FIGURE 3.9 Arteriovenous fistula. **A**, Femoral angiogram showing communication between the femoral artery and the vein (blue arrows). **B**, Three-dimensional reconstruction of a computed tomography scan showing communication between the common femoral artery (black arrow) and the common femoral vein (white arrow). AVF, Arteriovenous fistula; PFA, profunda femoris artery; SFA, superficial femoral artery. (**A**, Adapted from Bangalore S, Bhatt DL. Femoral arterial access and closure. *Circulation*. 2011;124(5):e147-e156. **B**, Reproduced with permission [open access journal] from Ozyüksel A, Doğan R. Iatrogenic femoral arteriovenous fistula with double connection between femoral artery and vein leading to high-output heart failure years after mitral and tricuspid valve replacement. *Case Rep Vasc Med*. 2013;2013:712089.)

and requires manual or mechanical compression, prolonged bed rest, and cessation of anticoagulation followed by observation and serial ultrasonography. A large pseudoaneurysm can be treated by ultrasound-guided manual or mechanical compression or ultrasound-guided thrombin injection (Figure 3.10B) into the pseudoaneurysm sac. Rarely, surgical repair may be required.

Artery Occlusion

Limb ischemia after femoral arterial cannulation is rare with an incidence of less than 0.8%.^{14,23,24} It is usually

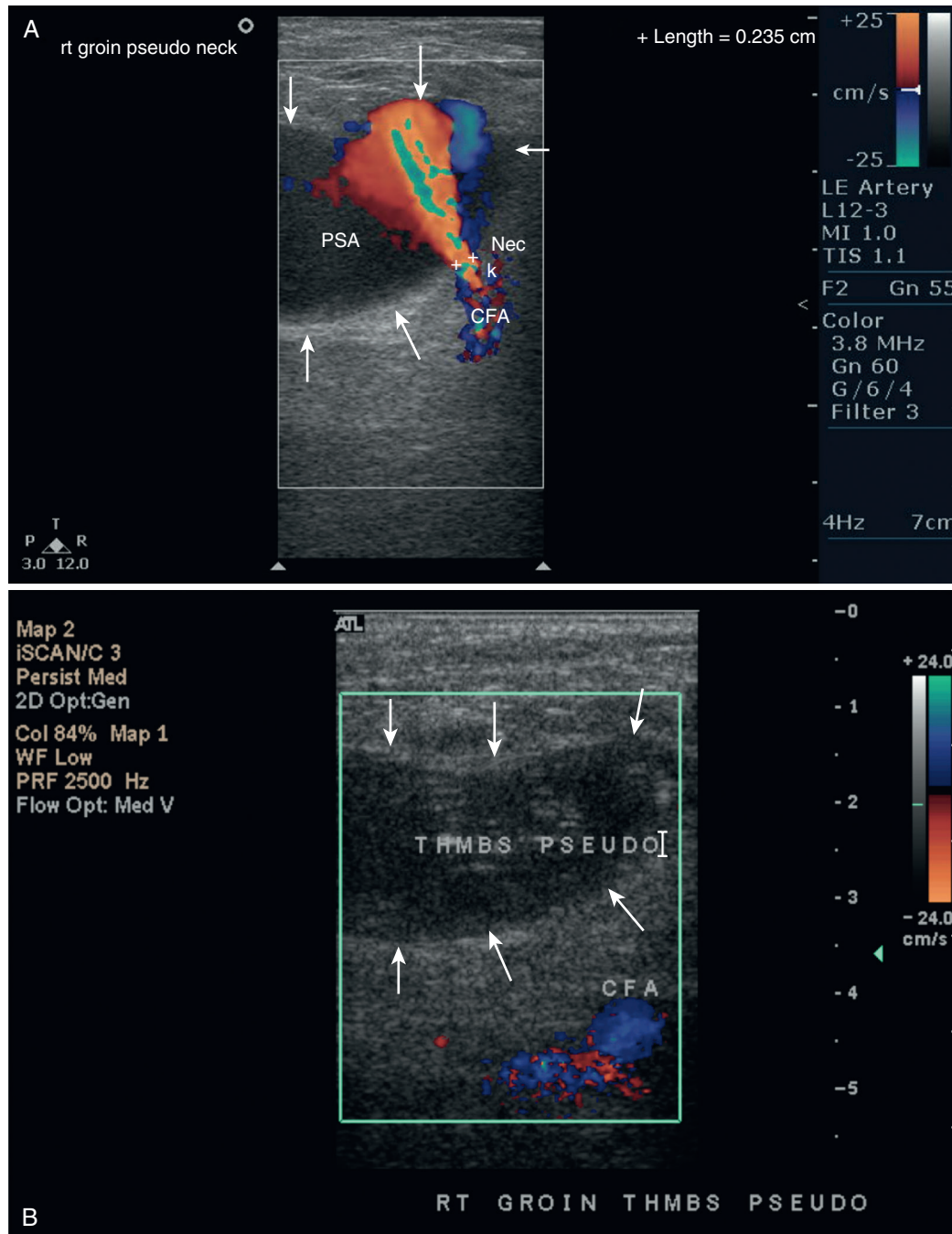


FIGURE 3.10 Pseudoaneurysm. **A**, Color Doppler ultrasound image showing a pseudoaneurysm (PSA, arrows) communicating with the common femoral artery (CFA) via a short neck. **B**, Color Doppler ultrasound image of a patient after ultrasound-guided thrombin injection showing a thrombosed pseudoaneurysm (arrows) with no communication with the CFA.

caused by occlusion of the artery by thromboembolism. Common risk factors include a small-caliber artery, peripheral vascular disease, the use of larger size sheaths, low cannulation into the superficial femoral or PFA, the use of a VCD with intraarterial components (e.g., Angio-Seal), or a sheath that is left behind for a prolonged period of time. In addition, digital ischemia may be caused by cholesterol emboli (Figure 3.12). Classic signs and symptoms include the five Ps: pain, pallor, paresthesia, pulselessness, and paralysis. The diagnosis is by Doppler ultrasonography studies. Angiography is needed to localize the site of occlusion. Treatment includes anticoagulation, contralateral

access, and angiography, with thrombectomy and possible angioplasty or stenting, directional atherectomy (for intraarterial deposition of collagen with Angio-Seal), or intraarterial fibrinolytic administration. In some cases, surgical thrombectomy with vascular bypass grafting may be required. In rare cases, ischemic complication can be caused by the use of a VCD such as Perclose or Angio-Seal (Figure 3.13). In addition to dislodgment of plaque by the footplate of these devices, intraarterial deposition of collagen (with Angio-Seal) or subintimal dissection of the CFA (with Perclose) has been described as the cause of ischemic complications.²⁷

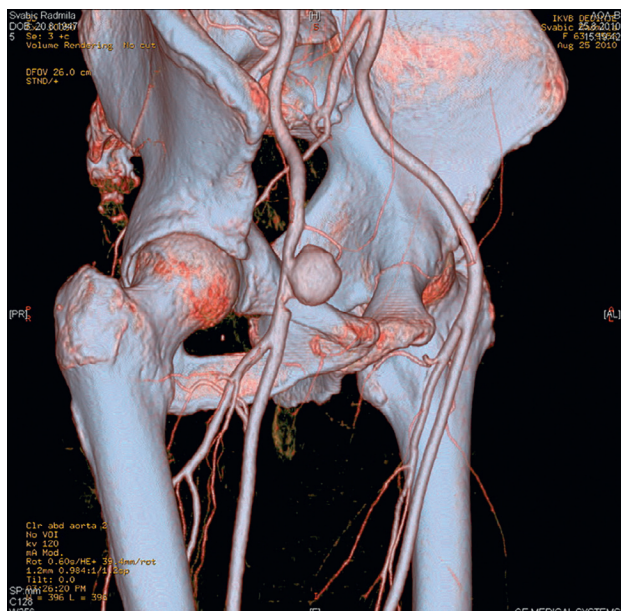


FIGURE 3.11 Pseudoaneurysm. Three-dimensional computed tomography reconstruction of a patient with femoral pseudoaneurysm (black arrow). (Reproduced with permission [open access journal] from Matic P, Babic S, Tanaskovic S, Jovic D, Radak D. Treatment of infected pseudoaneurysm of femoral artery after vascular closure device deployment: a practical solution. *Case Rep Vasc Med*. 2012;2012:292945.)



FIGURE 3.12 Cholesterol emboli. Peripheral embolic lesions in the toes. (Reproduced with permission from Dupont PJ, Lightstone L, Clutterbuck EJ, et al. Lesson of the week: cholesterol emboli syndrome. *BMJ*. 2000;321(7268):1065-1067.)

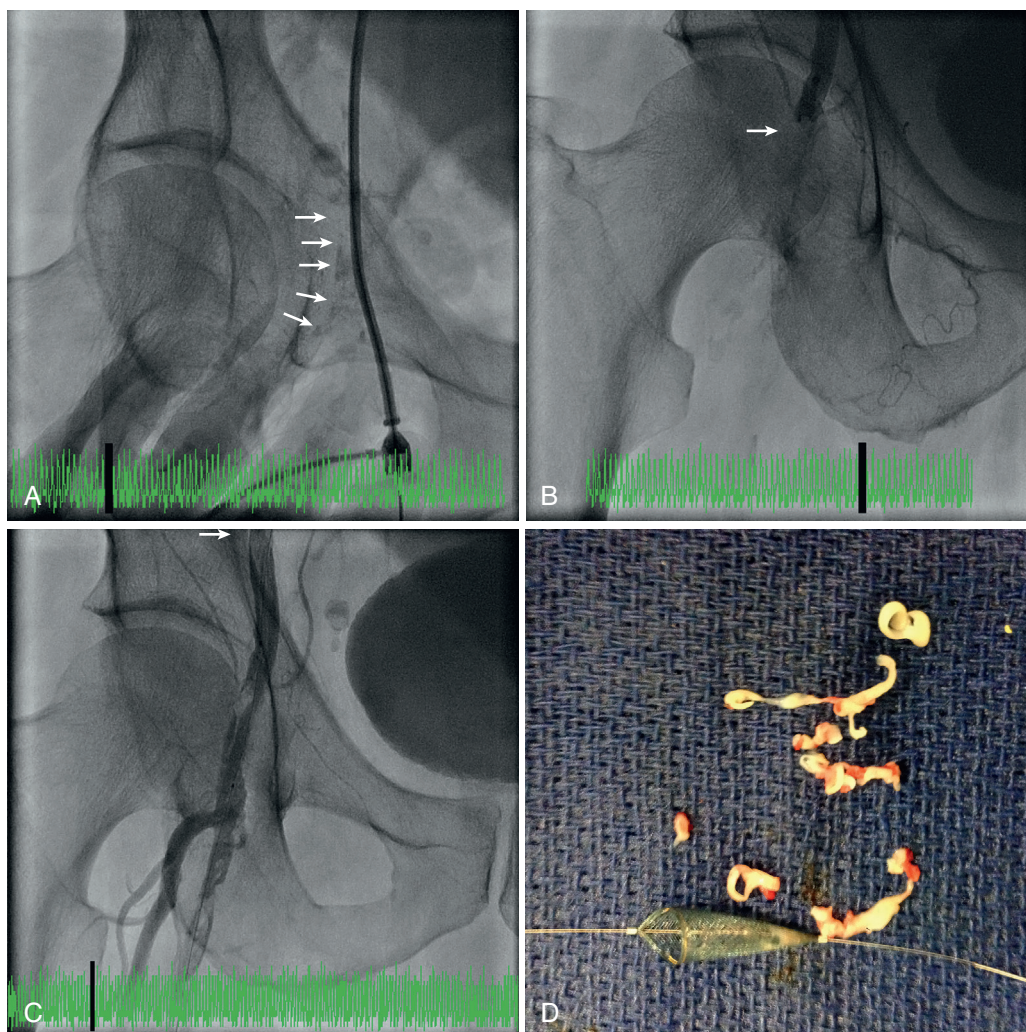


FIGURE 3.13 Femoral artery occlusion. **A**, Heavily calcified common femoral artery (white arrows). **B**, No flow at the site of calcification (white arrow) after deployment of the Angio-Seal device. **C**, Reestablishment of flow after wiring and thrombectomy showing thrombus at the site of calcification (white arrow). **D**, Collagen plug retrieved after atherectomy using the SilverHawk Plaque Excision system. (**A–C**, Courtesy of Dr. Sohah Iqbal, New York University School of Medicine, New York. **D**, Courtesy of Drs. Pawan Hari and Anvar Babaev, New York University School of Medicine, New York.)

Dissection

Femoral artery dissection is a rare (0.2%–0.4%) complication of femoral artery cannulation.²⁴ Risk factors include the presence of atherosclerosis in the CFA or the external iliac artery, vessel tortuosity, and dissection during advancement of the guidewire or during femoral angiography. The diagnosis is made during femoral angiography and most patients are asymptomatic. In rare cases, the patient presents with symptoms and signs of ischemic limb after the sheath is removed. Treatment includes observation because most dissections are retrograde and spontaneously heal. In rare cases, if ischemic complications arise, contralateral access and angiography and possible angioplasty or stenting or surgical repair should be considered.

Femoral Neuropathy

Femoral neuropathy is caused by injury to the femoral nerve during access or compression of the femoral nerve by a hematoma or pseudoaneurysm. The incidence is around 0.2%.²³ Patients present with pain or paresthesia at the femoral access site with radiation down the limb or with leg weakness. Physical examination may reveal focal neurologic signs, including decreased sensory perception, decreased motor strength, or decreased patellar tendon reflexes. Treatment should be aimed at the underlying cause (hematoma or pseudoaneurysm), treatment of symptoms, and physical therapy.

Groin Site Infection

Access site infection is rare (<0.1%)²³ but can be potentially serious, resulting in sepsis. Risk factors include obesity with folds of adipose tissue at the access site, presence of superficial infection at the site of entry, diabetes mellitus, compromised sterile technique during access or closure, prolonged indwelling sheath time, and use of a VCD. Patients present with pain, swelling, discharge at the access site, fever, or an increase in the white blood cell count. Treatment includes administration of antibiotics and symptomatic treatment for pain relief. In rare cases and especially when a VCD is used, surgical debridement with removal of any indwelling component of the closure device may be necessary. Infection associated with the VCD is an extremely serious complication that requires aggressive medical and surgical intervention and carries high rates of morbidity and mortality.²⁸ The majority of patients with infection present 7 to 10 days after deployment of the device and need prolonged antibiotic therapy (up to 28 days) and arterial debridement and reconstruction.

FEMORAL ARTERIAL ACCESS SITE CLOSURE

Introduction

Securing hemostasis after performing a procedure via the femoral arterial access is an important part of the procedure, and complications can be serious. The risk of complications (both ischemic and bleeding) is directly related to the duration the sheath is left in place. It is therefore recommended that the femoral arterial sheath be left in for the least amount of time possible and removed immediately

after diagnostic procedures if no anticoagulation was used. There are four ways of obtaining hemostasis after the procedure: (1) manual compression, (2) mechanical compression, (3) assisted compression devices or topical hemostasis accelerators, and (4) VCDs.

Manual Compression

Manual compression is considered the gold standard for obtaining hemostasis after femoral arteriotomy and is the most commonly used hemostasis technique worldwide. Correct technique is essential to ensure adequate hemostasis but also to minimize complications such as bleeding or hematoma and pseudoaneurysm formation. The femoral sheath should be removed immediately after diagnostic procedures if no anticoagulation is used or when the activated clotting time is less than 150 seconds to 160 seconds or the partial thromboplastin time is less than 45 seconds when heparin is used, 6 to 8 hours after the last enoxaparin dose, 2 hours after stopping bivalirudin, or when the fibrinogen level is greater than 150 mg/dL when fibrinolytics are used. VCD should be considered if the sheath is to be removed in a fully anticoagulated patient. The general principles of manual compression include application of pressure at the correct site and for adequate periods of time. It is important to note that the artery puncture site is 2 cm superior and medial to the skin entry site, and as such, manual compression should be applied over the arteriotomy site and not directly over the skin puncture site. The duration of compression varies with the size of the catheter and on other factors such as patient's blood pressure and anticoagulation status. A rough rule is to apply manual compression for 5 minutes for each 1 Fr, although effective hemostasis can be obtained for an arterial sheath of 4 or 5 Fr in under 10 to 15 minutes and for venous sheath of 8 or 9 Fr in under 5 to 10 minutes. Adjunctive use of a mechanical compression device should be considered for compressing the access site for an extended period of time. The steps in manual compression are outlined in [Table 3.3](#). The advantage of manual compression is that it is associated with the lowest complication rate, and there is no foreign body left behind either intraarterial or extraarterial.²⁹⁻³¹ The disadvantage includes the need to wait for prolonged periods of time for anticoagulation to wear off before sheath removal, discomfort (both to the operator and the patient) during the sheath removal, prolonged period of bed rest after manual compression with longer time to ambulation, complications caused by ineffective compression (bleeding, hematoma, pseudoaneurysm, or AVF formation), and a potential increase in time to hospital discharge. More recently, ambulation as early as 1 hour after removing a 5-Fr^{12,32} or 1.5 hours after removing a 6-Fr sheath^{33,34} has been shown to be safe, thereby decreasing the time to hospital discharge.

Mechanical Compression

Mechanical compression involves the use of a mechanical device for external compression to obtain hemostasis. This can be used as a stand-alone device (no manual compression) or as an adjunct to manual compression for an

TABLE 3.3 Steps in Manual Compression for Femoral Artery Hemostasis

Preprocedure
• Check to ensure that adequate time has passed since the last anti-coagulation (as described in the text). • Ensure that the patient's blood pressure is not high and treat as needed. • Connect the patient to the monitor to assess heart rate continuously and blood pressure every 1–2 minutes. • Lower the bed level to the comfort of the operator (prevents the operator from straining his or her back). • Move the patient close to the side edge of the bed next to the operator removing the sheath (prevents the operator from straining his or her back). • Notify the nurse of the procedure to be ready with medications in case of vasovagal reaction. • Inspect the access site for any signs of existing hematoma. • Assess the distal pulses (dorsalis pedis and posterior tibial).
Procedure
• Clean the sheath and surrounding area with antiseptic solution. • Remove the sutures holding the sheath in place. • Bleed back the sheath to expel any thrombus. • Palpate the artery cranially (1–2 cm cranially) from the skin exit site of the sheath using three fingers. • Apply gentle pressure over the arteriotomy site (not the skin exit site) with the three fingers, remove the sheath, and allow for back bleed from the arteriotomy site to flush any remaining thrombus. Too much pressure at this stage can compress or crush the sheath and strip clots that may have formed. • Continue compression along the length of the artery using the three-finger approach. Alternately, place a rolled gauze along the length of the artery and apply pressure using the palm of the hand. • Lock the elbows of both arms and lean forward using the upper body weight to apply pressure. • The duration of compression varies with the size of the catheter (rough rule is to hold for 5 minutes for every 1 Fr). However, for arterial sheaths of 4 or 5 Fr, hemostasis may be achieved in less than 10–15 minutes and for venous sheaths smaller than 8 or 9 Fr in under 5–10 minutes. • Remove the venous sheath (if any) 5 minutes after removing the arterial sheath (prevents arteriovenous fistula formation). • During the last 5 minutes of compression, let the pressure down to 25% of initial pressure. • For any symptoms and signs of vasovagal reaction (nausea, vomiting, diaphoresis, bradycardia, or hypotension), decrease pressure on the artery (while ensuring hemostasis) and administer atropine and/or intravenous fluids if needed. • Assess and record the distal pulses (dorsalis pedis and posterior tibial).
Postprocedure
• Clean the area with an antiseptic solution. • Cover with a small transparent dressing (opaque dressing can obscure bleeding or hematoma and should be avoided). • Monitor for any signs of bleeding (access site inspection, heart rate, and blood pressure monitoring). • Instruct the patient to remain on bed rest with the corresponding leg straight. A rough rule for the duration is 1 hour for each French size of the sheath (e.g., 6 Fr = 6 h). • Instruct the patient not to lift his or her head up or strain during coughing because any increase in intraabdominal pressure can cause the arteriotomy site to open up, resulting in bleeding.

extended period of compression. There are two main types of mechanical compression: the C-clamp (CompressAR, Advanced Vascular Dynamics and Clamp Ease, Pressure Products) and pneumatic (FemoStop, Radi Medical Systems AB, St. Jude Medical). The C-clamp consists of a flat metal base, a pivoting metal shaft attached to the base, an adjustable arm lever with arm slide, and an upper and lower arm lock mechanism to hold the desired level of pressure (Figure 3.14A). The preprocedural considerations

are similar to those outlined in Table 3.3. Raise the arm to the top of the stand and rotate the shaft so that the arm is pointed away from the patient. Position the base of the C-clamp beneath the bed mattress and directly below the patient's hip on the site of the femoral sheath. Rotate the C-clamp arm into the desired position. Attach a disposable translucent pad to the tip of the C-clamp arm. Palpate the access site 1 cm to 2 cm proximal to the skin entry site and gently lower the C-clamp arm into position, ensuring that the sheath is center to the disc at the V-notch just outside the perimeter of the disc (Figure 3.14B). Do not place anything between the pad and the skin, including gauze pads. Lock the top lever. With one hand on the arm lever preparing to push down, use the other hand to remove the sheath and immediately apply enough pressure from the arm lever to obtain adequate hemostasis after ensuring adequate bleed back to flush remaining thrombus. Tighten the lever with adequate pressure to ensure hemostasis while at the same time ensuring that the peripheral pulse is not fully obliterated (Figure 3.14C). If bleeding is noticed, increase pressure as needed. If pulse is obliterated, ensure that this does not last beyond 2 to 3 minutes. When it is time to release compression, gradually raise and lower the arm lever to release pressure at small increments and check the site for any bleeding. If bleeding is noticed, press down on the arm lever until hemostasis is obtained. Repeat the procedure until the C-clamp can be fully removed without any bleeding. Postprocedure care is similar to that outlined in Table 3.3.

Pneumatic compression devices such as the FemoStop use a small, transparent, inflatable dome; an adjustable belt placed underneath the patient's hips; and a pump with a manometer to adjust pressure to an optimal level (Figure 3.15A). The preprocedural considerations are similar to those outlined in Table 3.3. Position the belt underneath the patient's hips in line with the puncture site, ensuring that the length of the belt is equal on either side of the hip (Figure 3.15B). Check the pedal pulses and record them in the patient's chart. Position the dome over the arteriotomy site (1–2 cm cranial and medial to the skin puncture site) and attach the belt to either end, making sure that the arch is level and square across the groin area (Figure 3.15C). Retract the sheath far enough to allow the hub to be free from underneath the dome. Pull the belt straps on either end to ensure that the arch is perpendicular to the femoral arteriotomy site. If a venous sheath is used, inflate the dome 20 to 30 mm Hg and remove the venous sheath before removing the arterial sheath. Inflate the dome 60 to 80 mm Hg, remove the arterial sheath, and quickly increase pressure in the dome 10 to 20 mm Hg greater than the patient's systolic blood pressure or until hemostasis is achieved. After a maximum of 3 minutes of suprasystolic pressure, lower the pressure to maintain a palpable pedal pulse while ensuring hemostasis. Postprocedure monitoring is as outlined in Table 3.3. After an appropriate duration of compression, deflate pressure 10 to 20 mm Hg every 2 to 3 minutes until it is zero. If bleeding ensues, inflate 10 to 20 mm Hg or until hemostasis is obtained and wait for 10 minutes before starting to wean off the pressure. When hemostasis is obtained, dress the site with a transparent sterile dressing as outlined

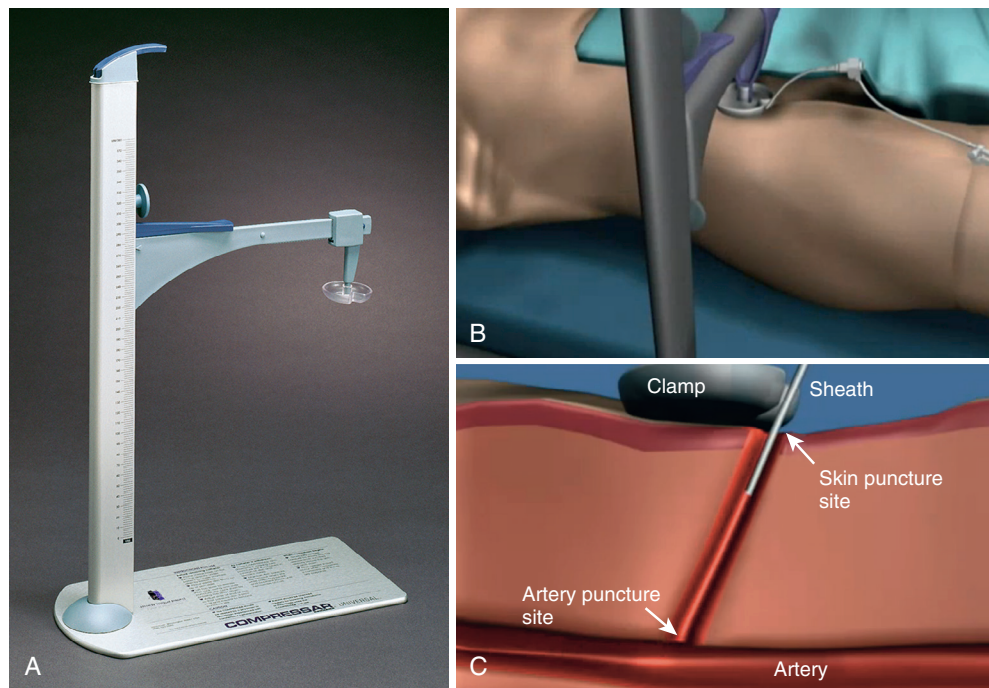


FIGURE 3.14 **A**, C-clamp (CompressAR, Advanced Vascular Dynamics) showing a flat metal base, pivoting metal shaft, adjustable arm level, and translucent pad attached to the tip of the C-clamp arm. **B**, C-clamp use technique. The C-clamp arm is lowered into position, ensuring that the sheath is positioned center to the disc at the V-notch just outside the perimeter of the disc. **C**, C-clamp use technique. The C-clamp is positioned such that the clamp is above the artery puncture site (arrow) and not the skin puncture site (arrow). (Reprinted with permission from Advanced Vascular Dynamics™, © 2014. All rights reserved.)

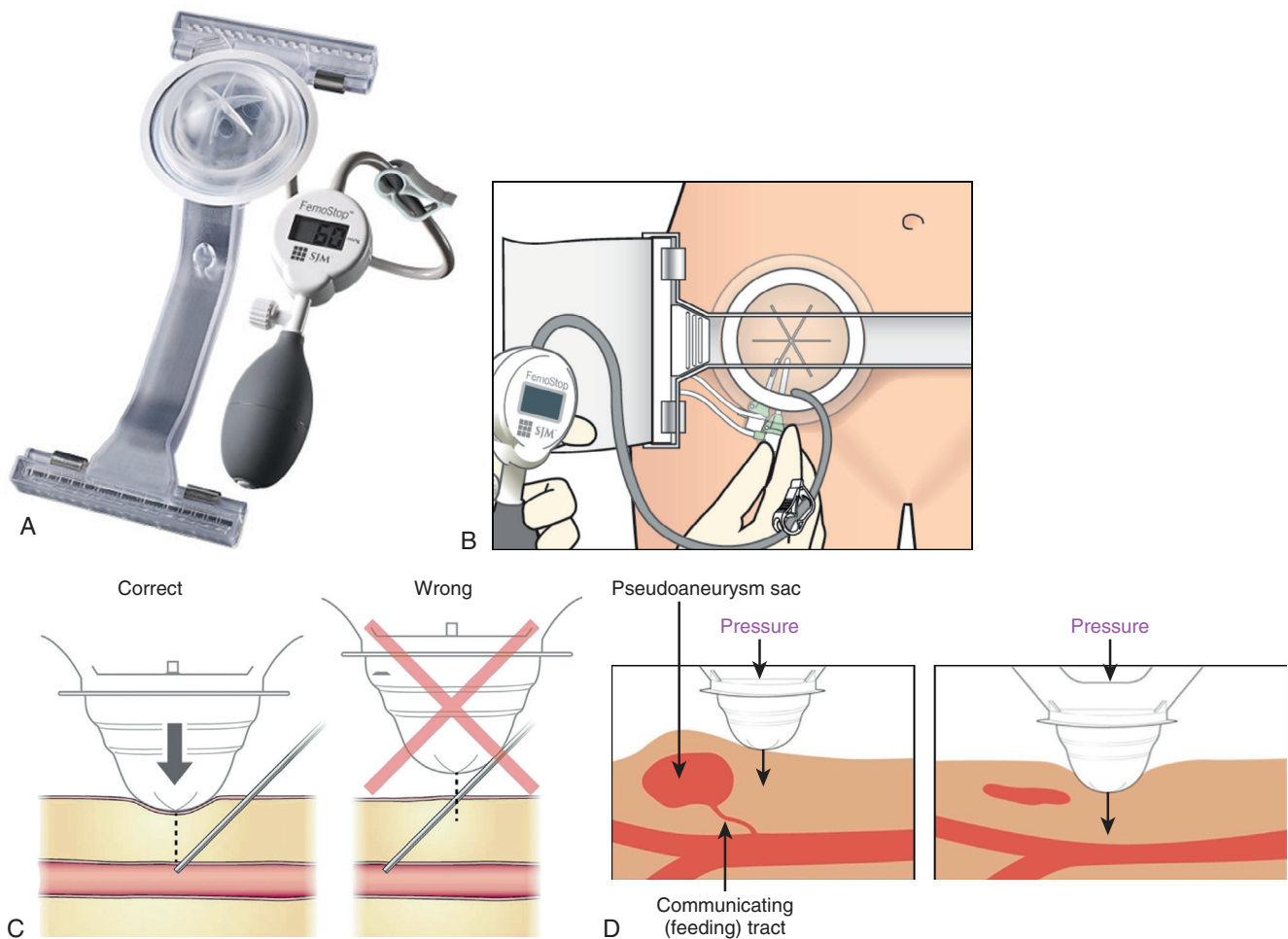


FIGURE 3.15 **A**, FemoStop (St. Jude Medical) device. **B**, FemoStop device use technique. Withdraw the femoral sheaths partially out and position the belt underneath the patient's hips in line with the puncture site, ensure that the length of the belt is equal on either side of the hip, and connect it to the FemoStop device such that the hubs of the sheath are outside the bulb of the device. **C**, FemoStop device use technique. The bulb is placed over the arterial puncture site and not the skin puncture site. **D**, FemoStop device use for treatment of pseudoaneurysm. The bulb is placed over the site of the communicating tract under ultrasound guidance, and pressure is applied for a prolonged period. (Reprinted with permission from St. Jude Medical™, © 2014. All rights reserved.)



in Table 3.3. The FemoStop is generally more comfortable for the patient than either manual compression or the C-clamp; direct contact with the blood is less; and the manometer allows for accurate control of pressure, potentially permitting patent hemostasis. In addition, it is also approved for ultrasound-guided compression of pseudoaneurysm (Figure 3.15D).

Assisted Compression Devices and Topical Hemostasis Accelerators

These consist of topical agents that hasten local clotting at the puncture site and are used along with manual or mechanical compression. The preprocedural considerations are similar to those outlined in Table 3.3. After cleaning the area around the sheath with antiseptic solution, palpate the artery 1 to 2 cm superior and medial to the skin puncture site. Apply firm pressure at the arteriotomy site (not the skin puncture site) and place the hemostasis patch over the puncture site. Ask the patient to take a deep breath in and then exhale while simultaneously the sheath is removed, allowing for back bleeding from the tissue tract to help expel any remaining thrombus. The bleeding also helps activate the hemostatic agent on the patch. After 3 minutes of occlusive pressure over the arteriotomy site, slowly release pressure while maintaining firm pressure directly over the puncture site and hemostasis pad. Apply sterile gauze and transparent dressing over the pad after hemostasis is obtained. These devices can potentially reduce the duration of manual compression. The commonly available topical hemostasis accelerators are listed in Table 3.4. The efficacy of topical hemostasis accelerators has been compared with manual compression alone in small, randomized trials with variable results, and there are no robust data to suggest that they shorten the time to ambulation.³⁵⁻³⁷

Vascular Closure Devices

Vascular closure devices, first introduced in the 1980s, are an effective alternative to both manual and mechanical compression after angiography. They function by mechanical closure of the arteriotomy site and are usually deployed in the catheterization laboratory even in a fully anticoagulated patient. Data from more than 1.8 million PCI procedures in the United States indicate that VCD is used in more than 60% of patients and is therefore the predominant modality to obtain hemostasis in the United States.²⁴ Early studies showed an increased risk of vascular complications with VCDs compared with manual compression.^{28-30,38-41} However, other studies have either shown equivalent efficacy^{31,42} or superiority of these devices in reducing the risk of complications compared with manual compression.⁴³⁻⁴⁶ In the largest series so far, data from more than 1.8 million PCI procedures demonstrated a significantly lower bleeding or vascular complication rate with Angio-Seal, Perclose, StarClose, Boomerang Closure Wire, and hemostasis patches compared with manual compression alone.²⁴ Of note, all types of hemostasis strategies including manual compression showed reduced

TABLE 3.4 Topical Hemostasis Accelerator

PRODUCT NAME	ACTIVE AGENT	MECHANISM OF ACTION
CELOX Vascular (Advanced Vascular Dynamics)	Chitosan	A natural polysaccharide that works independent of the body's normal clotting mechanisms
D-Stat Dry (Vascular Solutions)	Thrombin based	Thrombin-based agent that accelerates clotting; other versions have silver chloride for an anti-microbial barrier
HemCon Patch PRO (Hemcon)	Chitosan derivative with an antibacterial barrier	Positive ionic charge of the polymer attracts and binds red blood cells, promoting hemostasis; also provides an antibacterial barrier; does not contain procoagulants and is effective on anticoagulated patients
Neptune Pad (Biotronik)	Calcium alginate	Facilitates clotting cascade while providing an anti-microbial barrier
QuikClot (Z-medica)	Kaolin	Kaolin activates the clotting cascade and platelet adhesion
Scion Clo-Sur Plus PAD (Merit Medical Systems)	Polyprolate acetate (form of chitosan)	Positive ionic charge of the polymer attracts and binds red blood cells, promoting hemostasis
StatSeal ADVANCED (Medline)	Topical hemostatic powder	Stimulates the body's natural clotting cascade
Syvek Patch, PS, NT (Marine Polymer Technologies)	Poly-N-acetylglucosamine	Accelerates clot formation through red blood cell and platelet aggregation; localized vasoconstrictive effect
V + Pad (Angiotech)	D-glucosamine	Stimulates the body's natural clotting cascade

complication rates over time, perhaps an attestation to improvement in technology, awareness, or both. The advantages of these devices are reduction in the time to hemostasis, early patient mobilization, decreased hospital length of stay, facilitation of outpatient PCI, same-day discharge, and improvement in patient satisfaction.^{45,47-52} The disadvantages of these devices are the costs associated with them and various complications as discussed later. In an analysis of 23,813 patients undergoing coronary interventional procedure, the risk of VCD failure (defined as unsuccessful deployment or failure to achieve immediate access site hemostasis) was highest with the StarClose device (9.5%) followed by the Perclose device (6.1%), with the lowest rate being that for the Angio-Seal device (2.1%).⁵³ In addition, patients with VCD failure had a significant increase in the risk of subsequent vascular complications, major (any retroperitoneal hemorrhage, limb ischemia, or any surgical repair) and minor (any groin bleeding, hematoma [≥ 5 cm], pseudoaneurysm, or AVF), compared with patients with successful deployment of a closure device.⁵⁴ This is likely because most VCDs are deployed in fully anticoagulated patients, and failure can result in serious complications. In addition, VCDs can

TABLE 3.5 Vascular Closure Device Used in Clinical Practice

ACTIVE APPROXIMATORS	PASSIVE APPROXIMATORS
Angio-Seal (St. Jude Medical)	Boomerang (Cardiva Medical)
AngioLink (Medtronic CardioVascular)	Duett (Vascular Solutions)
FISH (Morris Innovative Research)	Mynx (AccessClosure)
Perclose (Abbott Vascular)	VasoSeal (Datascope Corp)
StarClose (Abbott Vascular, Santa Clara, Calif.)	ExoSeal (Cordis Corporation)
SuperStitch (Sutura)	
Catalyst (Cardiva Medical)	
MANTA (Teleflex)	

Only FDA-approved devices are listed.

Adapted from Bangalore S, Bhatt DL. Femoral arterial access and closure. *Circulation*. 2011;124(5):e147-e156.

serve as a nidus for infection (see the section on groin infection).

The commonly available VCDs are listed in Table 3.5. There are many classification systems for VCDs based on the mode of action, whether a foreign body is left behind, and whether this foreign body is extraluminal or intraluminal or temporary versus permanent.^{7,55}

1. *Active approximators versus passive approximators:* Active approximators actively approximate the arteriotomy site with the use of an anchor and collagen plug (Angio-Seal, MANTA), suture (Perclose), or nitinol clip (StarClose). On the other hand, passive approximators passively seal the arteriotomy site using either a sealant or Gelfoam (Mynx, FISH [femoral introducer sheath and haemostasis], Exoseal) or thrombin, which facilitates clot formation.
2. *Foreign body versus no foreign body:* VCDs such as the Angio-Seal, MANTA, Perclose, StarClose, and Mynx all leave behind a foreign body (anchor, plug, suture, clip, sealant), which can potentially be a source for infection. Novel devices such as the AXERA Access Device (Arstasis) provide self-sealing access that creates shallow-angle, longer arterial access and are designed to obtain hemostasis without the implantation of a foreign body (Figure 3.16).⁵⁶ Similarly, the Cardiva Catalyst (Cardiva Medical) consists of a biconvex, low-profile Catalyst Disc that is deployed over a wire inside the artery, blocking the arteriotomy site. A biocompatible coating aids the natural hemostatic process in the tissue tract. After hemostasis is obtained, the disc is collapsed and removed from the body, leaving no part of the device behind (Figure 3.17).
3. *Extraluminal versus intraluminal:* Whereas VCDs such as StarClose and Mynx leave an extraluminal foreign body, Angio-Seal, MANTA and Perclose leave behind an intraluminal foreign body.
4. *Temporary versus permanent:* VCDs such as Angio-Seal, MANTA, and Mynx leave behind foreign body, which gets reabsorbed over a period of time. However, devices such as the Perclose and the StarClose leave behind a permanent foreign body.

Next we will discuss the four commonly used VCDs—the collagen plug-based (Angio-Seal), the suture-based

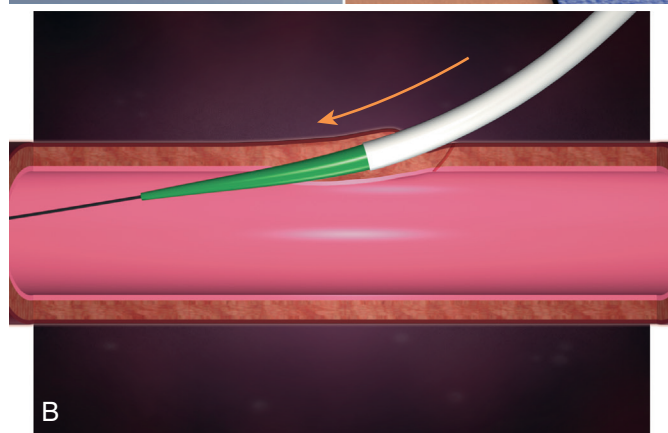
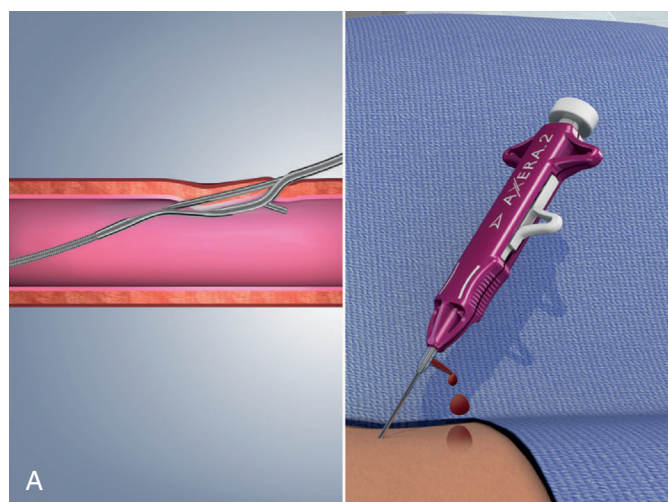


FIGURE 3.16 AXERA Access Device (Arstasis). **A**, The device creates a shallow-angle and longer arterial access and is designed to obtain hemostasis without the implantation of a foreign body. The image shows a needle passing through the wall of the artery at a shallow angle, creating a longer arterial access. **B**, Sheath entry into the artery at a shallow angle, resulting in longer arterial access. (Reprinted with permission from Arstasis™, © 2014. All rights reserved.)

(Perclose), the nitinol clip-based (StarClose), and the sealant-based (Mynx) devices.

Collagen Plug–Based Devices—Angio-Seal, MANTA

The Angio-Seal device (St. Jude Medical) is the most commonly used VCD in the United States, likely because of the short learning curve and high success rate (>97%).⁵⁷ It contains a small (2 × 10 mm), flat, absorbable rectangular anchor; an absorbable collagen plug; and an absorbable suture. It works on the principle of active approximation in which the intravascular anchor at the site of arteriotomy approximates the collagen plug (in the tissue tract) held together by a suture. The intravascular anchor, collagen plug, and the suture resorb in 3 months.

The device consists of (1) an insertion sheath with an arteriotomy locator, (2) a delivery device that contains the anchor and the collagen plug held together by the suture, and (3) a 0.035- or 0.038-inch 70-cm J-tipped guidewire. The insertion technique is outlined in Table 3.6 (Figure 3.18). The anchor, collagen plug, and suture all get reabsorbed over the next 90 days, leaving nothing permanently in the artery. Reaccess is therefore recommended after 90 days,

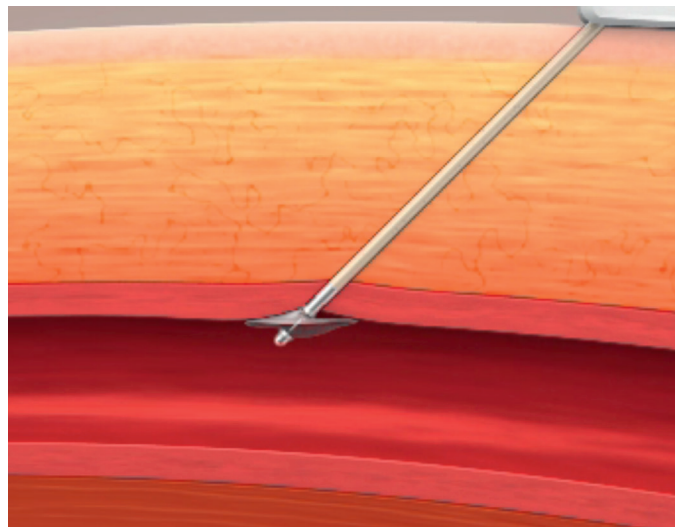


FIGURE 3.17 Cardiva catalyst device (Cardiva Medical). A biconvex, low-profile Catalyst Disc is deployed over a wire inside the artery blocking the arteriotomy site. A biocompatible coating aids the natural hemostatic process in the tissue tract. A newer version of the device called the VASCADE vascular closer system is now available. VASCADE VCS is an extravascular bioabsorbable femoral access closure system that leaves no permanent components behind and has demonstrated significant reduction in minor complications as compared with manual compression (1% vs 7%) in a multicenter, prospective randomized trial of 420 patients. Data from the Rapid Extravascular Sealing Via Percutaneous Collagen Implant (RESPECT) trial. (From Hermiller JB, Leimbach W, Gammon R, et al. A prospective, randomized, pivotal trial of a novel extravascular collagen-based closure device compared to manual compression in diagnostic and interventional patients. *J Invas Cardiol*. 2015;27(3):129-136) (Reprinted with permission from Cardiva Medical Inc.™, © 2014. All rights reserved.)

but if earlier reaccess is necessary, it is recommended to access 1 cm proximal to the prior cannulation site. Of note, the Angio-Seal device is available only in 6- or 8-Fr size. However, Angio-Seal has been used successfully to close large-bore (10- to 14-Fr) arteriotomy using a “double-wire” technique.⁵⁸ In this technique, two Angio-Seal J-tipped guidewires are inserted into the 10-Fr sheath, and the sheath is removed. The Angio-Seal device is deployed over one guidewire. If hemostasis is obtained after deployment of one Angio-Seal, the second wire is carefully removed while backpressure is maintained on the collagen plug. If hemostasis is not obtained after the first Angio-Seal device, a second device is then deployed over the second guidewire.⁵⁸

MANTA VCD (14 and 18 Fr) is specifically designed for large-bore closure (12–25 F4) and is based on the same principles as those of Angio-Seal (Figure 3.19). In the CHOICE-CLOSURE trial (comparison of a pure plug-based versus a primary suture-based vascular closure device strategy for transfemoral transcatheter aortic valve placement) of 516 patients who underwent transfemoral transcatheter aortic valve replacement (TAVR), the MANTA closure device resulted in higher major and minor vascular complications compared with Perclose ProGlide, driven by a higher rate of pseudoaneurysms and clinically significant hematomas.⁵⁹ However, there was a lower need for additional VCDs and a shorter time to hemostasis with MANTA.

TABLE 3.6 Steps in Insertion of the Angio-Seal Device^a

Preprocedure
- Obtain an ipsilateral femoral angiogram (30–45 degrees) to verify the position of the femoral arterial cannulation and to ensure there are no complications (dissection, perforation). - Factors unfavorable for the use of the Angio-Seal device include a small caliber of the artery (<4 mm); low cannulation (bifurcation, superficial femoral artery, profunda femoris artery); high cannulation (above the level of inferior epigastric artery); moderate to severe peripheral artery disease at the sheath insertion site; and an allergy to beef products, polyglycolic or polylactic acid polymers, or collagen products. - Clean the femoral artery cannulation site with an antiseptic solution. - Bleed back on the sheath to flush out any thrombus and flush the sheath with saline.
Procedure
- Choose a 6- or 8-Fr Angio-Seal device based on the femoral artery sheath size. - Insert the J-tipped guidewire into the sheath and remove the sheath over the wire. - Insert the arteriotomy locator into the insertion sheath until a click is heard. Insert this over the J-tipped guidewire and advance until a pulsatile flow is observed from the arteriotomy locator. - Withdraw the insertion sheath and the arteriotomy locator until the pulsatile flow ceases and advance just enough when the pulsatile flow starts again (optional). The insertion sheath is now distal to the arteriotomy site and within the artery lumen. - Hold the insertion sheath steady with one hand and remove the arteriotomy locator and guidewire by flexing upward. - Insert the delivery device through the insertion sheath and advance until it snaps fit. This deploys the anchor. - Hold the insertion sheath steady and pull the device cap back until it assumes a fully rear locked position. This sets the anchor. - Slowly withdraw the assembly until resistance is felt. The anchor is now up against the arterial wall. This also exposes the collagen plug. - Hold back the assembly and push the tamper tube down to push the collagen plug closer to the anchor. - A clear stop is exposed on the suture. Cut the suture below the clear stop and remove the tamper tube. - Cut the suture below the skin level, leaving behind as little of the suture as possible. - The Angio-Seal device is now deployed.
Postprocedure
- Check the femoral and distal pulse and document it in the chart. - Apply a small transparent dressing over the arteriotomy site. - The anchor, collagen plug, and suture will all get reabsorbed (over 90 days). - Reaccess at the site can be performed 90 days after the procedure. If reaccess is needed before this, consider reaccess 1 cm cranial or caudal to the puncture site.

^aFor more details, please see product information for use.

Collagen Plug–Based Devices—Mynx

The Mynx VCD (AccessClosure) is an extravascular closure device that uses a synthetic hydrogel (polyethylene glycol sealant) deployed outside the artery while a balloon occludes the arteriotomy site from within the artery. The hydrogel absorbs blood and other subcutaneous fluids and expands and adheres to the surface of the artery to achieve hemostasis, and the balloon is deflated and removed through the tract, leaving behind only the sealant. As such, no foreign body is left within the artery, and the sealant reabsorbs in 30 days. The device works on the principle of passive approximation.

The device consists of (a) a MynxGrip device including a balloon catheter and the sealant and (2) a 10-mL syringe for balloon inflation. It is indicated for vascular closure of sheaths sizes 5 to 7 Fr. The insertion technique is outlined

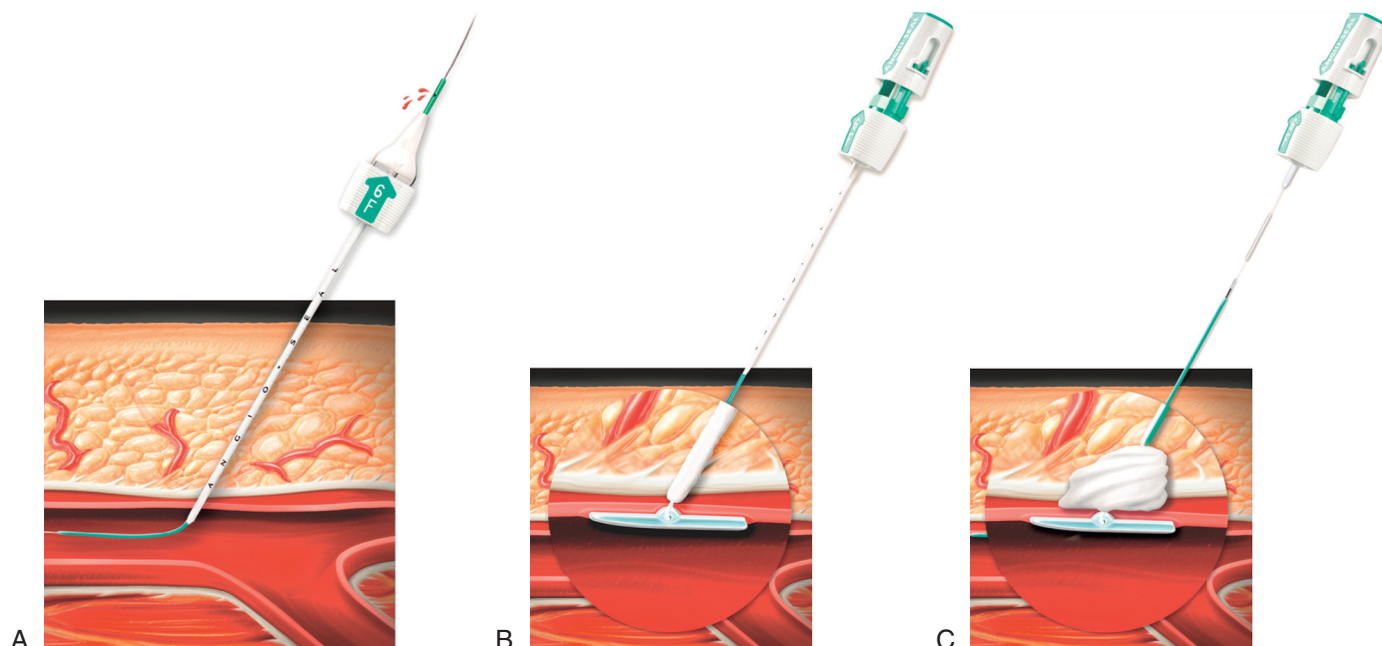


FIGURE 3.18 Angio-Seal device (St. Jude Medical) deployment technique. **A**, The Angio-Seal insertion sheath with an arteriotomy locator is exchanged for the femoral artery sheath over a guidewire and advanced until a pulsatile flow is noted from the arteriotomy locator. **B**, Deployment of the anchor. The collagen plug is also visible. **C**, The collagen plug is pushed closer to the anchor by a tamper tube. (Reprinted with permission from St. Jude Medical™, © 2014. All rights reserved.)

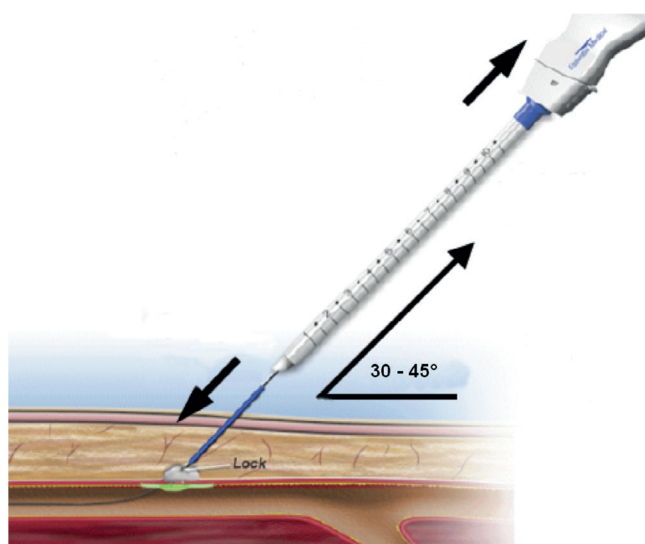


FIGURE 3.19 Manta Vascular Closure Device (Teleflex). A collagen plug seals the arteriotomy from the outside and is connected with the endoluminal bioresorbable toggle through van Gils L, De Jaegere PP, Roubin G, Van Mieghem NM. The MANTA vascular closure device: a novel device for large-bore vessel closure. *JACC Cardiovasc Interv.* 2016;9(11):1195-1196.)

in Table 3.7 (Figure 3.20). The device success rate is 91% to 93%, and the device leads to rapid hemostasis (mean time, 1.3 minutes) and ambulation (mean time, 2.6 hours).^{60,61}

Suture-Mediated Closure Devices

The Perclose ProGlide (Abbott Vascular) is a suture-mediated device that works on the principle of active approximation, leaving behind a monofilament nonabsorbable polypropylene suture. The 6-Fr ProGlide is designed for closure of 5- to 21-Fr sheaths, and the Prostar XL, which

uses two braided polyester sutures, is for closure of 8.5- to 24-Fr sheaths (CE Mark). For sheath sizes greater than 8 Fr, preclose technique with at least two ProGlide devices can be used. Perclose ProGlide and Prostar XL work on the principle of mechanical closure and are therefore not clot dependent.

The Perclose ProGlide device consists of (1) delivery device with a plunger, handle, guide, and sheath, containing the pretied suture knot; (2) a snared knot pusher; and (3) a suture trimmer. The Perclose ProStyle is the next generation design evolution of the ProGlide with higher tensile-strength needles for more complex, challenging anatomy; enhanced lubrication at the cuff of the foot to reduce the overall deployment force required to depress the plunger and deploy the needle; depth reference markers for both the device and suture trimmers; and enhanced visibility of the guidewire exit port for ease of re-access. The insertion technique is outlined in Table 3.8 (Figure 3.21). Compared with the Angio-Seal device, the Perclose device has a higher learning curve, a higher failure rate,^{57,62} and a longer time to hemostasis.⁶² However, the reported infection rate (~0.3%) is comparable to that with the Angio-Seal device.⁶³

For sheath sizes greater than 8 Fr, a preclose technique may be used with two or more ProGlide devices. After cannulating the femoral artery, insert a 6-Fr sheath and obtain femoral angiography to ensure that the anatomy is suitable for the use of a ProGlide device. Exchange the sheath over a wire and insert the first of the two ProGlide devices over the guidewire until the guidewire exit port of the device sheath is just about at the skin line. Remove the guidewire and then advance the device until brisk pulsatile blood flow is seen at the marker lumen. Rotate the device to approximately 30 degrees toward the patient's right

TABLE 3.7 Steps in Insertion of the MynxGrip Vascular Closure Device^a

Preprocedure
- Obtain an ipsilateral femoral angiogram (30–45 degrees) to verify the position of the femoral arterial cannulation and to ensure there are no complications (dissection, perforation). - Factors unfavorable for the use of the Mynx device include a small caliber of the artery (<5 mm), severe peripheral artery disease at the sheath insertion site, prior surgical procedure, stent placement or vascular graft in the common femoral artery, patients with bleeding disorders or uncontrolled hypertension, and those with morbid obesity. - Clean the femoral artery cannulation site with an antiseptic solution. - Bleed back on the sheath to flush out any thrombus and flush the sheath with saline.
Procedure
- Use the appropriate MynxGrip device—5 or 6/7 Fr based on the femoral artery sheath size. - Fill the locking syringe with 2–3 mL of saline, attach it to the stopcock, draw the vacuum, and then inflate the balloon until the black marker on the inflation indicator is fully visible. Check for any leaks in the balloon. Deflate the balloon and leave the syringe at neutral. - Insert the MynxGrip into the femoral artery sheath up to the white shaft marker. The balloon is now just distal to the femoral artery sheath. - Inflate the balloon using the locking syringe until the black marker on the inflation indicator is fully visible and close the stopcock. - Grasp the handle and withdraw the catheter until there are two points of tactile resistance. The first point is when the balloon abuts the distal end of the sheath and the second point is when the balloon abuts the arteriotomy site. - Open the stopcock on the procedure sheath. There should be no blood coming out, confirming hemostasis by the inflated balloon. - With slight back tension on the device, advance the shuttle until a definitive stop is felt. This advances the sealant into position. - Withdraw the femoral artery sheath until the shuttle locks in place while still holding back tension on the device. - Grasp the white tube at the skin level and advance until the green marker is fully exposed. This advances the sealant on to the arteriotomy surface. - Hold in place for up to 30 seconds. Then lay down the device for up to 90 seconds. - Lock the syringe to a full negative. Hold gentle pressure on the groin and open the stopcock to deflate the balloon. - Keep the advancer tube in place and remove the device. Remove the advancer tube and hold pressure for up to 60 seconds. - Assess for hemostasis and apply pressure if needed.
Postprocedure
- Check the femoral and distal pulse and document it in the chart. - Apply a small transparent dressing over the arteriotomy site. - The sealant dissolves in 30 days.

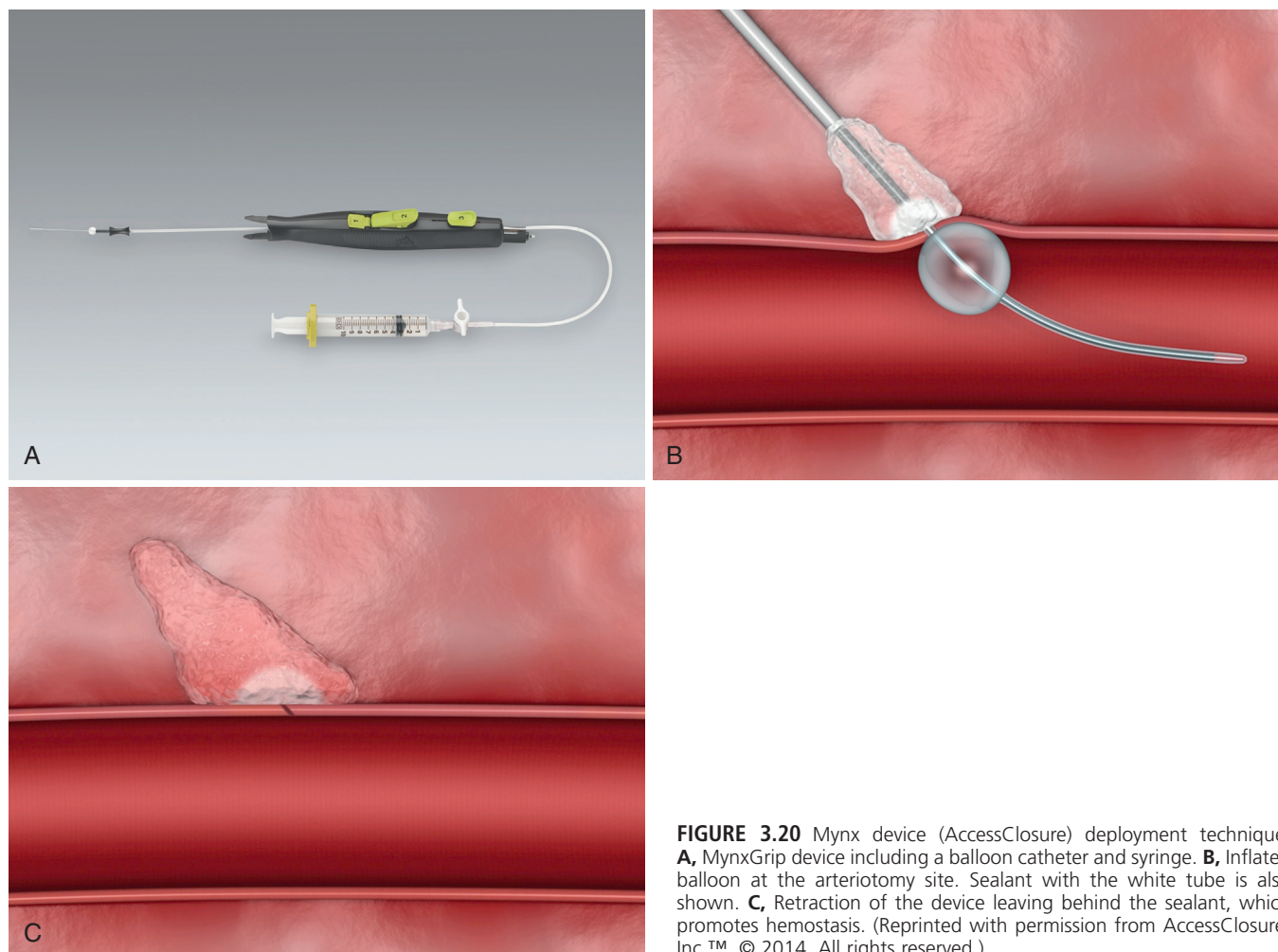
^aFor more details, please see product information for use.


FIGURE 3.20 Mynx device (AccessClosure) deployment technique. **A**, MynxGrip device including a balloon catheter and syringe. **B**, Inflated balloon at the arteriotomy site. Sealant with the white tube is also shown. **C**, Retraction of the device leaving behind the sealant, which promotes hemostasis. (Reprinted with permission from AccessClosure, Inc.™, © 2014. All rights reserved.)

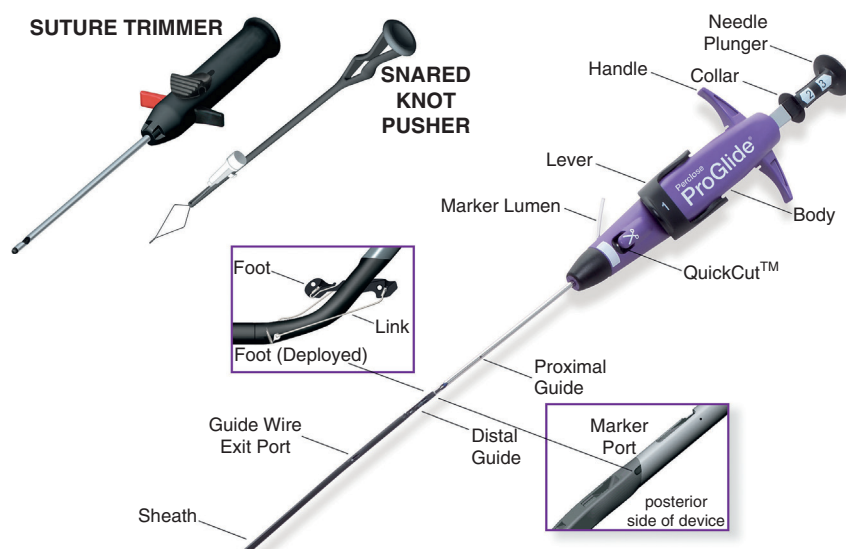
TABLE 3.8 Steps in Insertion of the Perclose Vascular Closure Device^a

Preprocedure
- Obtain an ipsilateral femoral angiogram (30–45 degrees) to verify the position of the femoral arterial cannulation and to ensure there are no complications (dissection, perforation). - Factors unfavorable for the use of the Perclose device include those with small femoral arteries (<5 mm), severe peripheral artery disease at the sheath insertion site, severe calcification at the insertion site, prior surgical procedure, stent placement or vascular graft in the common femoral artery, low cannulation (bifurcation, superficial femoral artery, profunda femoris artery), high cannulation (above the level of inferior epigastric artery), and cannulation at the femoral artery bifurcation. - Clean the femoral artery cannulation site with an antiseptic solution. - Bleed back on the sheath to flush out any thrombus and flush the sheath with saline.
Procedure
- Use the appropriate sized Perclose ProGlide for 5–21 Fr or ProStar for 8.5–10 Fr. - Insert a 0.035- or 0.038-inch J-tipped guidewire through the femoral artery sheath and remove the sheath. - Advance the Perclose device over the guidewire until the guidewire exit port is just about at the skin line. - Remove the guidewire and continue to advance the device until pulsatile blood flow is seen at the marker lumen. - Deploy the foot by lifting the lever on the body of the device. - Pull the device back until the foot is against the arterial wall (resistance is felt at this stage, and blood flow at the marker lumen ceases). - Stabilize the device by maintaining gentle traction and deploy needles by pushing on the plunger. - Pull back the plunger assembly to completely remove the plunger and needle from the body of the device and use the QuickCut suture trimming mechanism or a sterile scalpel or scissors to cut the suture from the anterior needle. - Relax the back tension of the device and bring the foot to its original closed position by pushing the lever down. - Retract the device to release the suture knot. Continue to retract until the two suture limbs are seen in the distal guide. Free the suture limb from the device. The blue suture limb is the rail suture, and the white suture limb is the lock suture. - Load the rail limb of the suture onto a snared knot pusher. - Wrap the rail suture limb around your left forefinger and bring down the knot pusher to the level of the Perclose device. - Remove the device completely with your right hand while pulling on the rail suture limb and advancing the knot pusher with the thumb of the left hand. - With the knot pusher held in position and keeping the rail suture limb taut, tighten the knot by pulling on the nonrail suture limb while being coaxial to the tissue tract. - Relax the pressure on the knot pusher and observe for hemostasis. If hemostasis is not achieved, advance the knot pusher and hold it down until hemostasis is achieved. Tighten the knot by pulling on the nonrail (white) suture limb. - Remove the knot pusher and use the knot trimmer to cut the excess length of the suture limbs.
Postprocedure
- Check the femoral and distal pulse and document it in the chart. - Apply a small transparent dressing over the arteriotomy site. - There is no reaccess restriction for the Perclose device.

^aFor more details, please see product information for use.

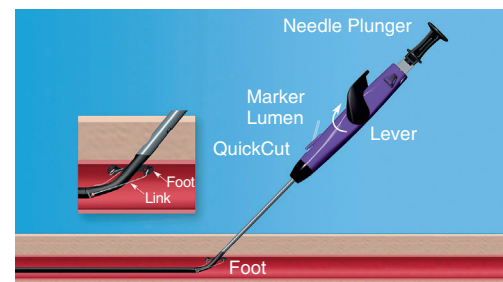
Perclose ProGlide[®]

Suture-Mediated Closure System



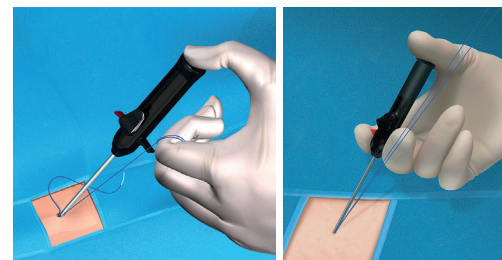
Illustrations are artist renditions. Not drawn to scale.
Courtesy of Abbott Vascular.
©2012 Abbott. All rights reserved. AP2937592-OUS Rev. A

A



For distribution outside the U.S. and Japan ONLY.
Illustrations are artist renditions. Not drawn to scale.
Courtesy of Abbott Vascular.

B ©2013 Abbott. All rights reserved. AP2938048-OUS Rev. A



For distribution outside the U.S. and Japan ONLY. Illustrations are artist renditions. Not drawn to scale.
Courtesy of Abbott Vascular.
©2013 Abbott. All rights reserved. AP2938048-OUS Rev. A

C

FIGURE 3.21 Perclose ProGlide device (Abbott Vascular) deployment technique. **A**, Component of the Perclose ProGlide device. **B**, Device advanced into the artery with pulsatile blood flow from the maker lumen. **C**, Using the snared knot pusher on the blue rail to push the knot down to the arteriotomy site. The *right panel* shows the suture trimmer that is placed on the suture limb, and the suture is trimmed as close to the arteriotomy site as possible. (Courtesy of Abbott Vascular, © 2012–2013. All rights reserved.)



side (approximately the 10 o'clock position), deploy the foot by lifting the lever, and gently pull back the device until resistance is felt and there is no more pulsatile flow at the marker lumen. While retracting the device gently, deploy the needles by pushing on the plunger assembly. Remove the plunger assembly and cut the suture limb using QuickCut or a sterile scissor or scalpel. Relax the device and return the foot to the closed position by pushing the lever down to the body of the device. Retract the device to release the pretied suture knot and continue to withdraw until the guidewire exit port is visible above the skin line. Gently pull out both the suture limbs from the distal end of the guide. Use a hemostat or clamp to hold the two suture limbs together and place it to a side. Reinsert the guidewire through the guidewire exit port. Remove the device while holding compression above the puncture site to maintain hemostasis. Insert the second ProGlide device over the guidewire and repeat the steps, now deploying the needle about 60 degrees to the first device (approximately the 2 o'clock position). The two suture limbs from the second device should be similarly clamped and placed on the opposite side to that of the first one without locking the suture knot. Insert the guidewire again through the guidewire exit port, remove the device, and exchange it for an appropriately sized femoral artery sheath. The procedure is then carried out through this sheath. At the end of the procedure, insert a J-tipped guidewire through the sheath. Insert the blue suture limb (rail limb) onto the snared knot pusher, wrap it around the left index finger, and advance the knot pusher with the thumb of the left hand onto the sheath. With pressure on the knot pusher onto the sheath from the left hand, remove the sheath with the right hand while pushing the knot pusher onto the guidewire. Do not lock or excessively tighten the knot while the guidewire is still in the vessel. Now free the second suture, insert the rail limb of the suture through a snared knot pusher, wrap it around the index finger of the left hand, and push the knot pusher down to the guidewire. Do not lock or excessively tighten the knot while the guidewire is still in the vessel. Assess for hemostasis. If hemostasis is not obtained, one more ProGlide device can be deployed, with this one facing the 12 o'clock position and repeating the steps. If hemostasis is achieved, push down on the knot pusher on one or both of the rail sutures and ask an assistant to remove the guidewire while advancing both pushers. Assess for hemostasis and tighten the knot by holding the rail suture limb steady, pulling the nonrail suture limb on both the wires, and trimming the suture limbs using a suture trimmer.

Using the preclose technique, successful hemostasis was achieved in 94% of patients undergoing percutaneous endovascular aortic valve repair in a meta-analysis of 36 studies and 2257 patients with 3606 arterial accesses. The complication rate was low (3.6%), and complications requiring open surgery were only 1.6%.⁶⁴ In addition, the technical success rate for sheath sizes 12 to 16 Fr has been shown to be around 99% and that for sheath size 18 to 24 Fr around 91%.⁶⁵ Compared with the Angio-Seal device, the risk of device failure was higher with the Perclose device.⁵⁴

Clip-Based Device—StarClose

The StarClose device (Abbott Vascular) uses a 4-mm nitinol clip deployed outside the arterial wall. The clip grasps the edges of the arteriotomy, drawing them together for closure. It thus works on the principle of active approximation, using a mechanical approximation without leaving behind any intravascular components. However, the clip is permanently left behind on the surface of the artery. The device is approved for closure of 5- to 6-Fr arteriotomies but has also been used with larger sheath sizes (7–8 Fr). The device success was 91% for 7-Fr and 90% for 8-Fr sheaths with major vascular complication rates of 4.1% and 2.5%, respectively.⁶⁶ Although not recommended for closure of cannulation at or near the femoral artery bifurcation, the device appears to be safe with a low rate of vascular complications (0.9%).⁶⁷

The device consists of the StarClose clip applicator and a 6-Fr exchange system. The clip applicator contains the nitinol clip, which is delivered through the exchange sheath. The insertion technique is outlined in [Table 3.9](#) ([Figure 3.22](#)). There are no reaccess restrictions for the StarClose device, although this has not been well studied. In porcine models, reaccess even through the center of the clip was feasible, and reclosure using a second StarClose device was successful with achievement of a secure closure.

Large-Bore Closure

Increasingly, large-bore access (10 Fr or greater) is used for procedures (e.g., TAVR, thoracic endovascular aortic repair) and for mechanical circulatory support (e.g., Impella, extracorporeal membrane oxygenation). Several techniques can be used to percutaneously close large-bore access sites using a combination of the devices discussed. The options for percutaneous large-bore closures include (1) MANTA device (for 12–25 Fr), (2) two Perclose devices using the preclose technique, (3) postclosure with two

TABLE 3.9 Steps in Insertion of the StarClose Vascular Closure Device

Preprocedure
• Obtain an ipsilateral femoral angiogram (30–45 degrees) to verify the position of the femoral arterial cannulation and to ensure there are no complications (dissection, perforation). • Factors unfavorable for the use of the StarClose device include those with small femoral arteries (<5 mm), sheath size larger than 6 Fr, severe peripheral artery disease at the sheath insertion site, severe calcification at the insertion site, prior surgical procedure, stent placement or vascular graft in the common femoral artery, low cannulation (bifurcation, superficial femoral artery, profunda femoris artery), high cannulation (above the level of inferior epigastric artery), cannulation at the femoral artery bifurcation, and hypersensitivity to nickel titanium. • Clean the femoral artery cannulation site with an antiseptic solution. • Bleed back on the sheath to flush out any thrombus and flush the sheath with saline. • Create a 5- to 7-mm skin nick at the sheath site and perform blunt dissection of the tissue tract using a hemostat clamp to accommodate insertion of the clip delivery tube into the tissue tract.

TABLE 3.9 Steps in Insertion of the StarClose Vascular Closure Device—cont'd

Procedure
• Exchange the femoral artery sheath over a J-tipped guidewire to the StarClose exchange sheath. • Remove the guidewire. • Insert the clip applicator into the hub of the exchange sheath and advance until the clip applicator locks into the sheath hub (a click is heard). • Retract the assembly by 3–4 cm and deploy the locator wings by pressing down on the plunger. • Initiate splitting of the sheath by pressing down on the thumb advancer and advance the assembly down to ensure that it can be delivered through the tissue tract. • Stabilize the device with the left hand at a 45-degree angle and retract until resistance is felt. The locator wings are now up against the arterial wall. • With continued stabilization with the left hand, press down on the thumb advancer to fully split the sheath all the way down until a click is heard. • Raise the clip applicator to a 60- to 75-degree angle and press down the assembly gently. Femoral artery pulsation can usually be felt at this stage. • With gentle downward pressure, deploy the clip by pressing on the deployment button. • Hold downward pressure for 2–3 seconds. • Apply counterpressure with the left hand with the index and middle fingers at the sheath exit site and slowly remove the assembly device. • Inspect for hemostasis and apply manual pressure as needed.
Postprocedure
• Check the femoral and distal pulse and document this in the chart. • Apply a small transparent dressing over the arteriotomy site. • There is no reaccess restriction for the StarClose device, although this is not well studied.

^aFor more details, please see product information for use.

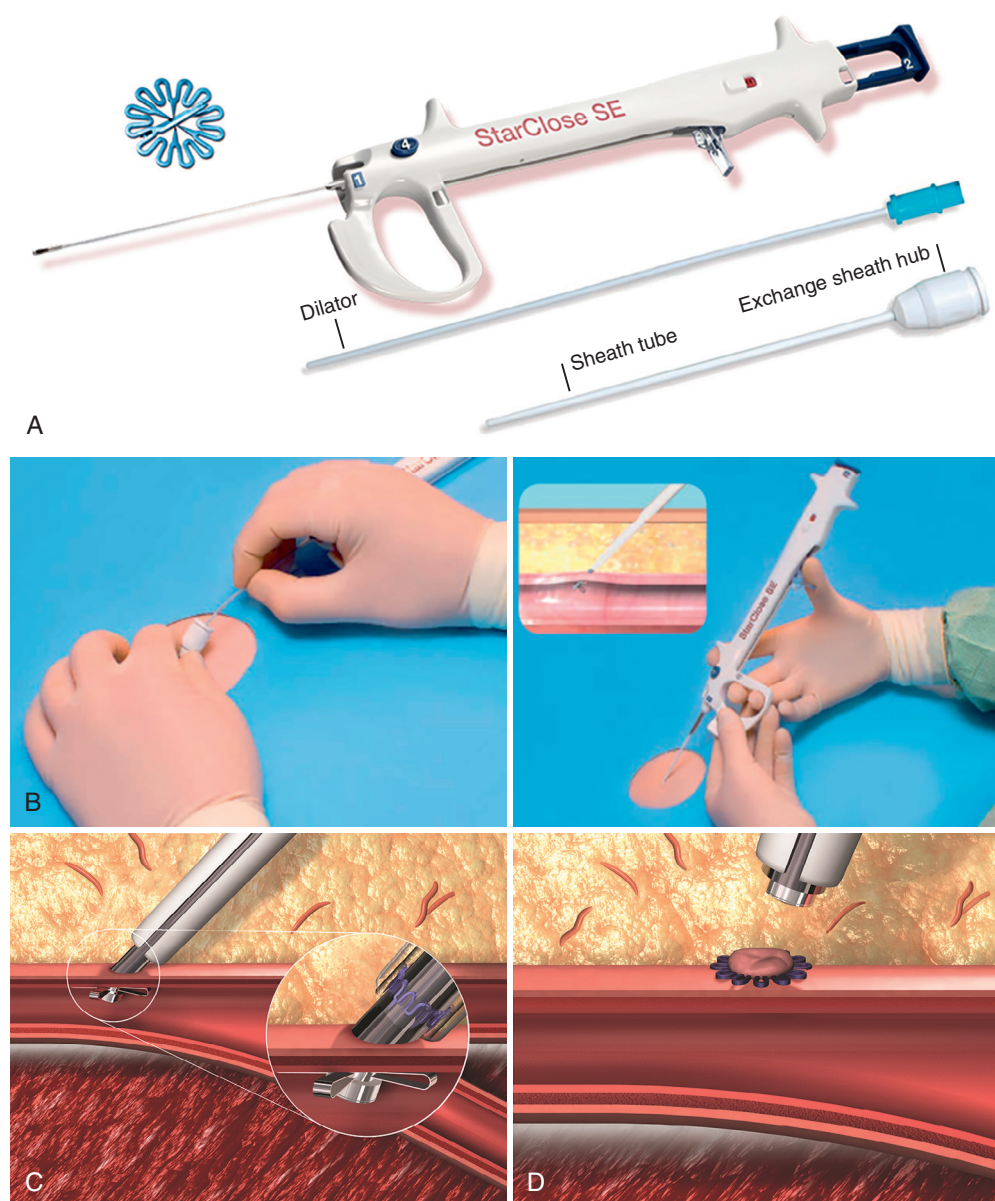


FIGURE 3.22 StarClose device (St. Jude Medical) deployment technique. **A**, Component of the StarClose device showing the nitinol clip, clip applicator, dilator, and sheath. **B**, Insertion of the clip applicator into the hub of the sheath. The *right panel* shows the technique for partial splitting of the sheath. **C**, The foot plate deployed at the arteriotomy site. The nitinol clip is shown inside the clip applicator. **D**, Deployment of the nitinol clip. (Reprinted with permission from St. Jude Medical™, © 2014. All rights reserved.)

Perclose devices or one Perclose device and one or two Angio-Seal devices, and (4) hybrid pre- and postclosure with one Perclose device deployed using the preclose technique and with postclosure using another Perclose or an Angio-Seal device. Typically, large-bore closure should be performed using the dry closure technique in which a balloon is inflated in the ipsilateral external iliac artery to low pressures (2–4 atm) while the access site is being closed. The dry closure technique helps in maintaining hemostasis at the time of closure, enhancing visibility, and preventing blood loss. In addition, dry closure techniques also allow for completion angiography to be performed to evaluate for any bleeding or ischemic complications at the site of the femoral access point or distal to it.

RADIAL ARTERIAL ACCESS AND CLOSURE

Introduction

The radial artery is a common site for arterial access for continuous blood pressure monitoring and for arterial blood gas measurement. Transradial access for coronary diagnostic procedures was introduced by Campeau⁶⁸ and for coronary interventional procedures by Kiemeneij et al.⁶⁹ Initially used as a “backup” access, transradial angiography and intervention are now the preferred alternatives to the traditional femoral approach worldwide, with rapid adoption in the United States.² In an analysis of more than 2.8 million coronary procedures performed in the United States, 16.1% of procedures, accounting for one in six procedures in 2012, were performed via the transradial route.² This is the predominant and preferred approach in many countries in Europe and Asia.⁷⁰ In addition to use for diagnostic and interventional coronary procedures, transradial access has been used to treat patients with peripheral artery disease or renal artery disease and for carotid intervention.^{71,72} The advantages of radial access for coronary procedures include reduced bleeding even with aggressive use of anticoagulation and antiplatelet therapies, reduced vascular complication rates, reduced cost, rapid ambulation, reduced length of stay, and increased patient satisfaction compared with the femoral access.^{2,73,74} In the Radial Vs femoral access for coronary intervention (RIVAL) trial, 90% of patients randomized to undergo the transradial approach reported preference for the same approach if a repeat procedure was needed, as opposed to 49% in the transfemoral arm.⁷⁵ As discussed previously, bleeding and vascular complications are major sources of morbidity and mortality.⁷⁶ However, a reduction in mortality rate with radial access when compared with femoral has only been shown in high-risk subgroups such as those with ST-segment elevation myocardial infarction,^{75,77-79} without increase in door-to-balloon times. Disadvantages of radial access include longer fluoroscopy time and radiation exposure,^{80,81} a steeper learning curve,⁸² limitation of guide catheter size, access failure or crossover, and complications related to the access site such as radial artery occlusion. In addition, in patients with a left internal mammary artery graft, the procedure can be challenging, especially if the right radial artery is used. However, the procedure can be safely performed using the left radial access.⁸³ Studies have shown that the gap between radial

and femoral approaches for access-site crossover, procedure time, and radiation exposure decreases with increasing operator volume and experience.^{73,84,85} Table 3.10 compares radial and femoral arterial access for coronary angiography and intervention.

Anatomic Considerations

Knowledge of the anatomy of the radial artery and the circulation of the hand is important for proper radial artery cannulation and to troubleshoot complications. The radial artery originates from the brachial artery below the elbow and runs on the lateral aspect of the forearm underneath the supinator longus muscle to the wrist, where it lies on top of the styloid process of the radius bone and the scaphoid bone. The artery then passes across the base of the fifth metacarpal bone and joins the deep communicating branch of the ulnar artery to form the deep palmar arch. The superficialis branch of the radial artery joins the palmar part of the ulnar artery to complete the superficial palmar arch. At the region of the styloid process, the radial artery is superficial, has a diameter of 2 to 3 mm, and is not adjacent to other neurovascular structures, making it an ideal site for radial artery cannulation.

Preprocedural Considerations

Although radial access can be performed safely in the majority of patients, it should be avoided in patients with Raynaud’s syndrome, thromboangiitis obliterans (Buerger’s disease) (increased risk of radial artery occlusion), known carpal tunnel syndrome, skin infection at the insertion site, or ipsilateral hemodialysis fistulae and in those with full-thickness burn over the insertion site. Before radial artery cannulation, palpating the radial artery and testing for collateral circulation or patency of the palmar arch of the hand are recommended. This can be performed by either the Allen test or the Barbeau test. In addition, a thorough history and physical examination, a review of laboratory and medication data and a review of prior angiograms should be performed when available, as outlined in the section on femoral artery access.

Modified Allen Test

Originally described by Dr. Edgar Van Nuys Allen in 1929, the Allen test is a simple bedside visual test to assess for collateral circulation and dual circulation via the palmar arch of the hand (Figure 3.23A). Occlude both the radial and the ulnar artery at the wrist. Ask the patient to forcefully clench the hand several times to expel blood from the hand. Ask the patient to then open the hand avoiding wrist and finger hyperextension or wide separation of digits (this can result in a false-positive or a falsely abnormal test result). The hand should appear blanched (Figure 3.23B). Release pressure over the ulnar artery and record the time it takes for maximal blush in the palm (Figure 3.23C). If the color returns within 5 to 9 seconds, the result of the modified Allen test is considered negative (normal), and radial artery cannulation can be performed safely. If not, the test result is considered positive (abnormal). To date, there is no consensus regarding the optimum cutoff time

TABLE 3.10 Comparison of Radial and Femoral Arterial Access for Coronary Angiography and Intervention

VARIABLE	RADIAL ACCESS	FEMORAL ACCESS
Anatomical Features		
Vessel caliber (mm)	2–3	6–10
Vascular course	Variable	Constant
Vessel location in relation to skin	Constant, superficial	Variable, related to body habitus
Nearby neurovascular structures	No	Yes
Procedural Features		
Procedural success	Marginally lower than for femoral access	Marginally higher than for radial access
Procedural time	Comparable	Comparable
Contrast load	Comparable	Comparable
Fluoroscopy time	Marginally longer than for femoral access	Marginally shorter than for radial access
Choice of sheath sizes	Restricted	Unrestricted
Learning curve	Longer than for femoral access	Shorter than for radial access
Crossover to alternative arterial access	Higher than for femoral access	Lower than for radial access
Internal mammary artery graft cannulation	Variable	Simple
Complications		
Access site bleeding	Lower than for femoral access	Higher than for radial access
Access vessel occlusion (%)	≤30	≤5
Access site pseudoaneurysm (%)	0.05	≤5
PCI Outcomes		
Rate of MACEs	Comparable	Comparable
Mortality rate	Reduced in STEMI more than for femoral access	Increased in STEMI more than radial access
Patient Care		
Patient preference	Higher than for femoral access	Lower than for radial access
Time to ambulation	Immediate	2–6 h
Length of hospital stay	Shorter than for femoral access	Longer than for radial access

MACE, Major adverse cardiovascular events; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Data from Byrne RA, Cassese S, Linhardt M, et al. Vascular access and closure in coronary angiography and percutaneous intervention. *Nat Rev Cardiol*. 2013;10(1):27-40.

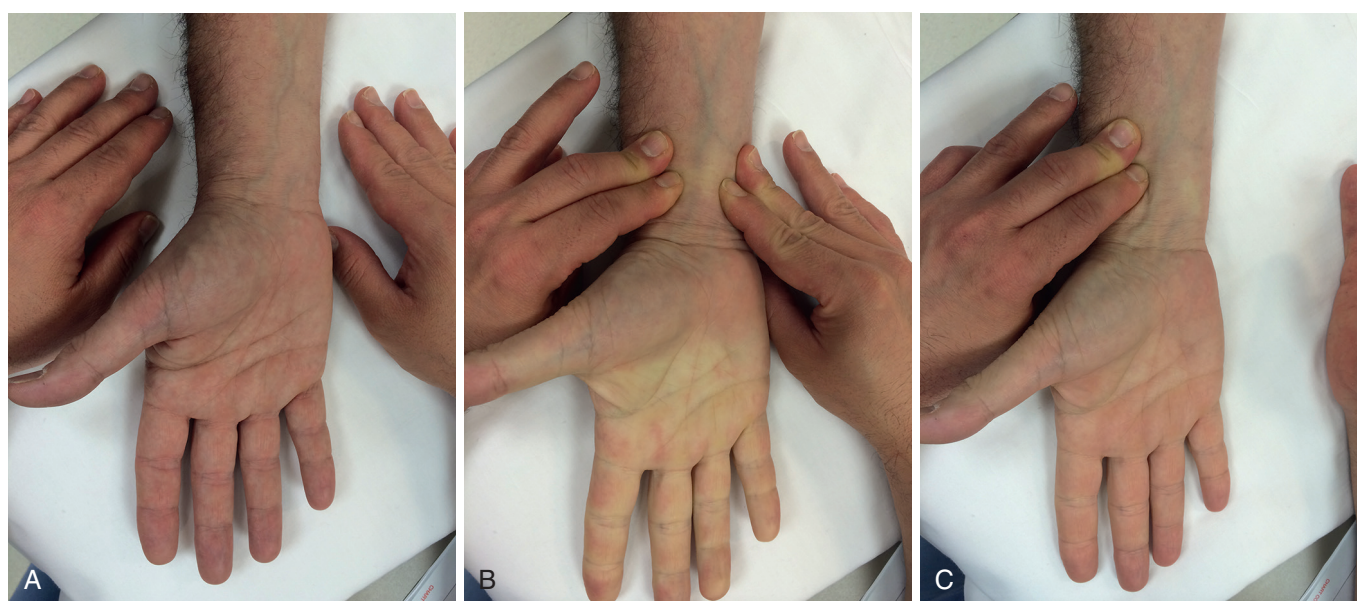


FIGURE 3.23 Modified Allen test to assess dual circulation of the hand. **A**, At baseline before compression of the radial and ulnar arteries. **B**, Blanching of the hand after compression of the radial and ulnar artery and after opening and closing the hand to expel blood. **C**, Release of the ulnar artery and blushing of the palm within 5 to 9 seconds, indicating a normal modified Allen test result. (Courtesy of Dr. John Coppola, New York University School of Medicine, New York.)

for a positive modified Allen test. It is preferable to use the term “normal” or “abnormal” because the negative or positive connotation may create confusion. The results of the Allen test should be recorded in the patient’s chart. The disadvantage of the Allen test is that it is more subjective, and several conditions can result in false-positive or false negative results.

Barbeau Test

Originally described by Gerald Barbeau in 2004,⁸⁶ the Barbeau test is an objective way of assessing for the ulno-palmar arterial arch with the use of pulse oximetry and plethysmography using a pulse oximeter. Place the plethysmography sensor on the index finger or the thumb of the upper extremity to be tested and observe the oximetry waveforms. Compress both the radial and ulnar arteries at the wrist for 2 minutes. The response to the ulnar artery release can be graded as the following: type A, no damping of pulse tracing immediately after radial artery compression; type B, damping of pulse tracing; type C, loss of pulse tracing followed by recovery of pulse tracing within 2 minutes; or type D, loss of pulse tracing without recovery within 2 minutes (Figure 3.24). The Barbeau test is found to be more sensitive than the Allen test.⁸⁶ In the modified Barbeau test, both the radial and ulnar arteries are compressed, resulting in a flat line on the plethysmography. The ulnar artery pressure is now realized, and return of the plethysmography waveform is indicative of good ulnar circulation (Figure 3.25).

The role of the Allen and Barbeau tests to predict the risk of ischemic complications after radial artery cannulation is controversial, and some experts believe postprocedural “patent hemostasis” is more important. An abnormal

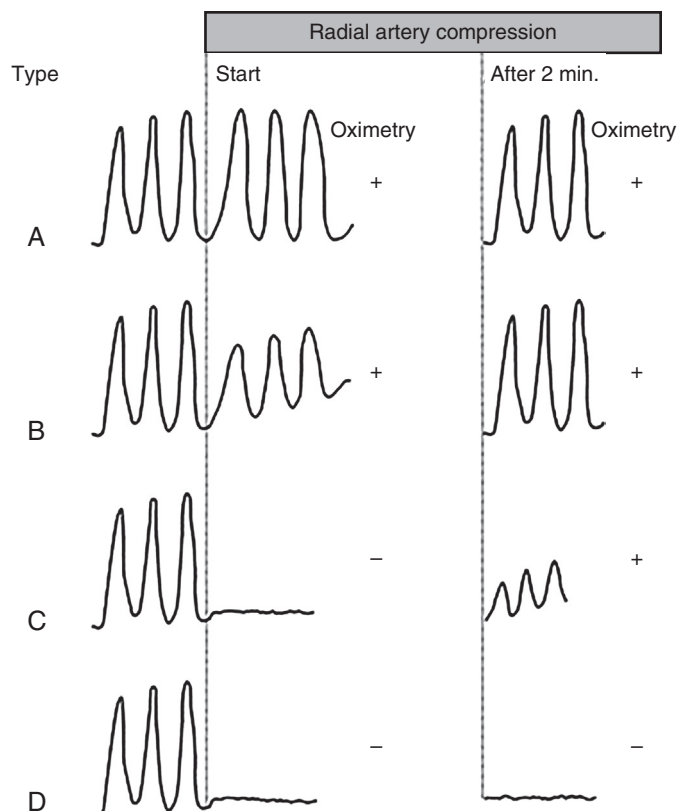


FIGURE 3.24 Barbeau test to assess dual circulation of the hand. Types A to D based on the original description by Barbeau. (Reproduced with permission from Barbeau GR, Arsenault F, Dugas L, Simard S, Larivière MM. Evaluation of the ulno-palmar arterial arches with pulse oximetry and plethysmography: comparison with the Allen’s test in 1010 patients. *Am Heart J*. 2004;147(3):489-493.)

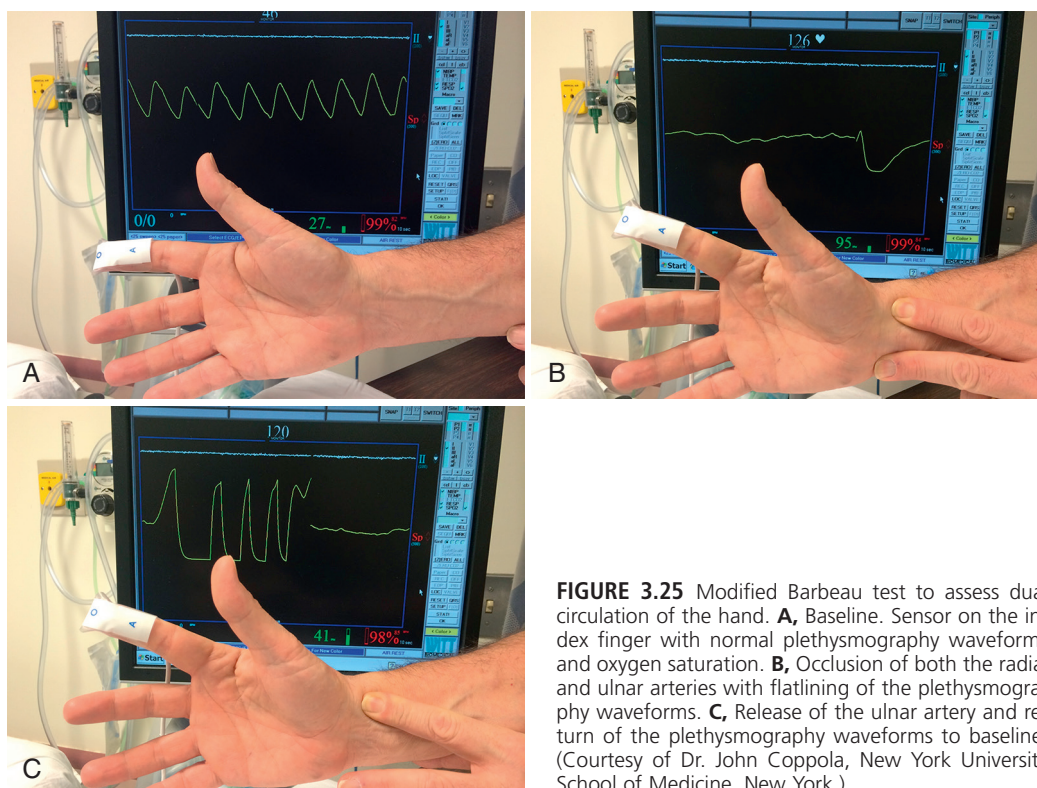


FIGURE 3.25 Modified Barbeau test to assess dual circulation of the hand. **A**, Baseline. Sensor on the index finger with normal plethysmography waveforms and oxygen saturation. **B**, Occlusion of both the radial and ulnar arteries with flatlining of the plethysmography waveforms. **C**, Release of the ulnar artery and return of the plethysmography waveforms to baseline. (Courtesy of Dr. John Coppola, New York University School of Medicine, New York.)

Allen or Barbeau test result may not necessarily indicate poor distal blood flow as shown by photoplethysmography,⁸⁷ fluorescein dye injection,⁸⁸ or thumb capillary lactate levels (as noted in the RADAR [Should Intervention Through Radial Approach be Denied to Patients With Negative Allen's Test Results] trial).⁸⁹ Moreover, the test assesses for collateral circulation via the palmar arch but other routes of collateral circulation also exist (via the interosseous artery). In addition, in patients with an abnormal test result who had a radial artery harvested for a bypass graft, no postoperative hand ischemia has been reported.⁹⁰ However, reports of ischemic injury have been reported even after a normal Allen test result.⁹¹ Ischemic injury after radial cannulation can also be caused by distal embolization or nerve compression. They are therefore not useful for determining the safety of radial access.¹¹

Procedural Considerations

Before the commencement of the procedure, a “time-out” should be performed to verify the patient’s identity, review the patient’s medical history and indications for the procedures, review the laboratory data, and confirm that the patient has provided written informed consent. The patient is then prepared and draped under sterile conditions.

Positioning

A number of arm boards or radial boards have been devised to assist in proper positioning of the patient’s arms for adequate radial access and to ensure comfort to the patient during the procedure. With the patient in a supine position, the arm should be maintained in a neutral position with the palm up and the wrist exposed. The access site should be clipped of hair if present. The wrist should be hyperextended to 30 degrees using a roll of gauze or towel and the hand and forearm secured to the board using tape (Figure 3.26). The arm should then be prepared

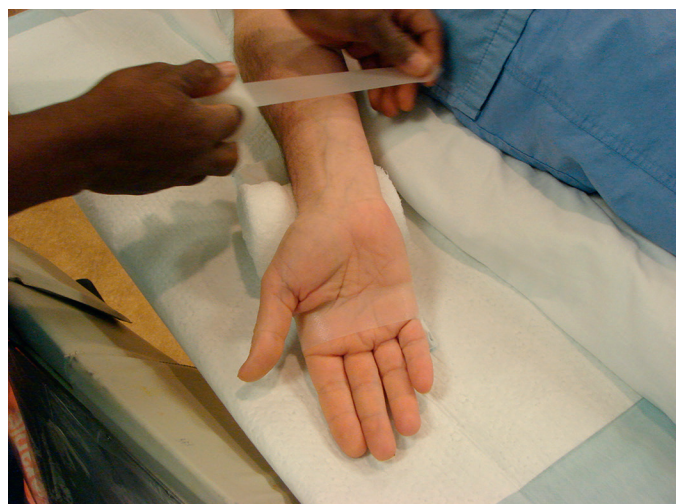


FIGURE 3.26 Positioning of the right hand for transradial access. A rolled gauze or towel is placed underneath the patient’s wrist to hyperextend it. (Courtesy of Dr. John Coppola, New York University School of Medicine, New York.)

and draped under sterile conditions. Some operators prepare the femoral site for “backup,” although this is rarely needed with more experienced operators.

Conscious Sedation and Local Anesthesia

Conscious sedation is administered with the use of a sedative (e.g., Versed) and an analgesic (e.g., fentanyl). Local anesthesia (e.g., lidocaine) is administered at the site of the radial artery using a 25-gauge needle or an insulin syringe to first create a dermal bleb. The amount of local anesthesia to be administered must be sufficient to provide comfort for the patient while not obliterating the radial artery pulsation. Care must be taken not to inject lidocaine into the artery because it can cause serious arrhythmias.

Technique

The radial artery can be cannulated using a 20- to 21-gauge needle. Specialized access kits are now available. Some of the access kits have a 21-gauge needle, and others have a microcatheter over a metal needle. The ideal puncture site for the radial artery is 2 to 3 cm proximal to the flexor crease of the wrist. If the pulse is not easily palpable, distal compression of the radial artery close to the palmar crease can increase the pulse amplitude at the more proximal site of puncture. Access can be obtained either with a through and through puncture (often preferred) (Video 3.1) or an anterior wall puncture (Video 3.2). With the through-and-through puncture technique, the needle with the microcatheter is advanced into the artery at a 30- to 45-degree angle until a flash of blood is seen (Figure 3.27A and B). The needle is then advanced through the posterior wall of the artery until the flash stops (see Figure 3.27B). The needle is then removed from the microcatheter, and the microcatheter is slowly withdrawn until pulsatile blood flow is seen (Figure 3.27C). The 0.018- or 0.021-inch guidewire is then inserted and the microcatheter exchanged for the appropriate size sheath with the dilator (Figure 3.27D). It may sometimes be necessary to perform a skin nick before advancement of the sheath, especially for sheath sizes greater than 5 Fr. Care should be taken to ensure that the bevel of the scalpel is facing up and away from the artery to prevent accidental transection of the radial artery. The dilator and the guidewire are then removed, the sheath flushed with saline, and an intraarterial vasodilator cocktail (verapamil or diltiazem or nitroglycerin) administered.⁹² Hydrophilic sheaths are generally used to minimize trauma and vasospasm. In addition, an anticoagulant such as unfractionated heparin or bivalirudin should be administered to prevent radial artery thrombosis.⁹³ The recommended regimen is intraarterial or intravenous unfractionated heparin at a dose of at least 50 U/kg up to a maximum of 5000 U.⁹⁴ In patients with heparin-induced thrombocytopenia, bivalirudin should be used.⁹⁴

Closure and Postprocedural Care

Closure

Similar to that of the femoral artery, the radial artery sheath should be left in place for the shortest duration required to minimize complications. Before removal of the sheath, the sheath should be back bled to flush out thrombus

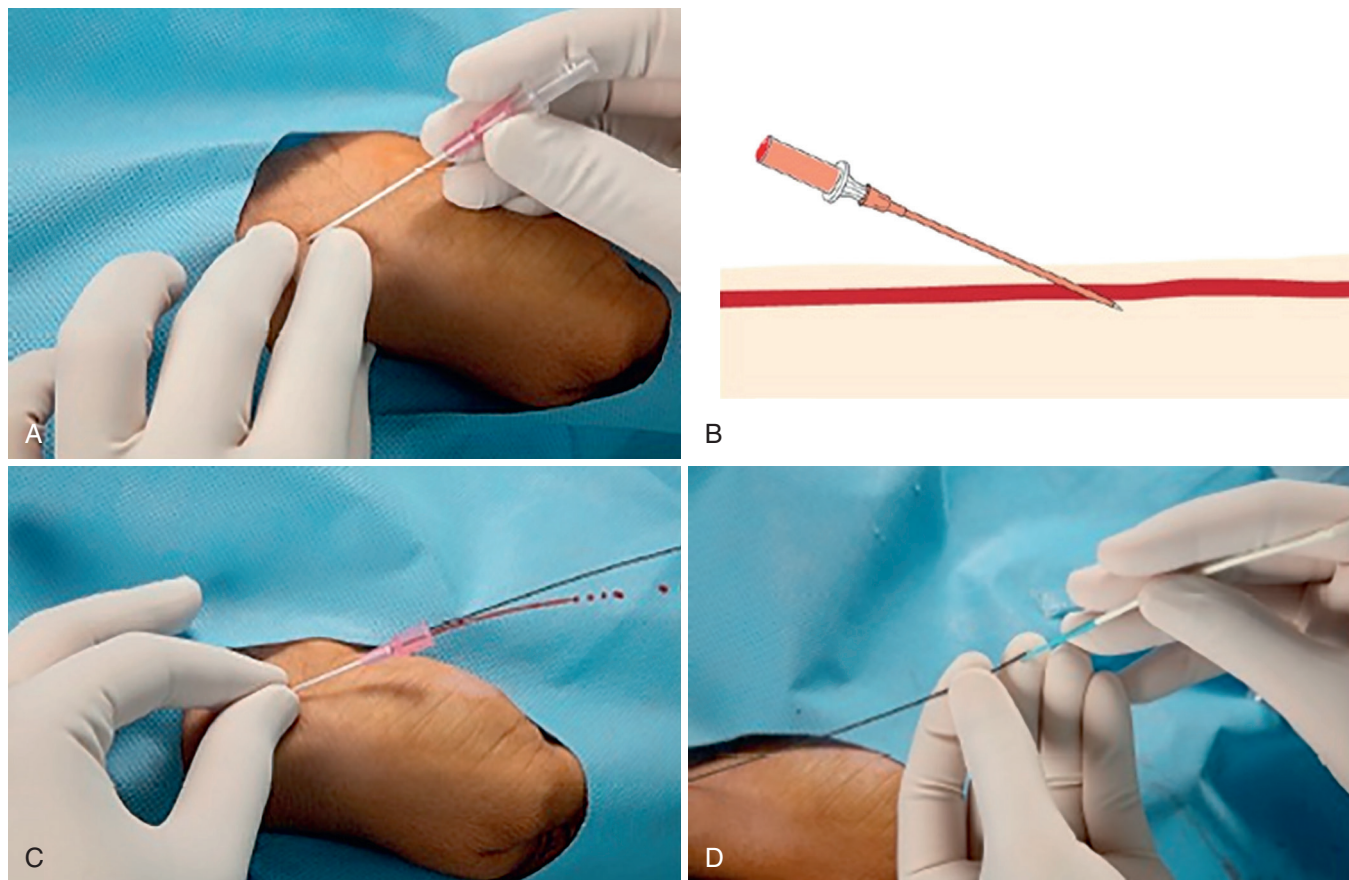


FIGURE 3.27 Transradial access. **A**, The ideal puncture site is 2 cm to 3 cm proximal to the crease of the wrist. The artery should be entered at a 30- to 45-degree angle. **B**, Through-and-through puncture technique. When a flash is seen upon entry of the artery, the needle is advanced, puncturing the posterior wall until no blood flow is seen at the needle hub. **C**, The needle is removed, and the microcatheter is slowly advanced back until pulsatile blood flow is seen. A guidewire is inserted. **D**, The microcatheter is exchanged for an appropriate size sheath over the guidewire. (Reproduced with permission from Patel T, Shah S, Rihal C, et al. *Patel's Atlas of Transradial Intervention: the basics and beyond*. Malvern, PA: HMP Communications LLC; 2012.)

and flushed with saline. Closure can be obtained by manual compression or by using specialized devices that maintain pressure on the wrist. The TR band is one such device, which consists of a transparent band with a dual compression balloon. Before application of this device, the introducer sheath should be withdrawn by 2 to 3 cm (Video 3.3). The green marker on the TR band is aligned 2 to 3 mm proximal to the puncture site, and the strap is tightened with the adjustable fastener (Figure 3.28). The syringe should be filled with 18 mL of air (maximal volume allowed) and attached to the TR band. Inject half the volume into the TR band balloon and remove the sheath with one hand while injecting the rest of the air with the other. Now slowly withdraw air 1 cc at a time until a flash of blood is seen at the puncture site. Now inject 1 to 2 cc of air to obtain hemostasis. Excess blood can be wiped away from underneath the band with sterile gauze. The TR band assures adequate hemostasis without compromising blood flow of the radial artery. Keep the syringe with the patient for later use during deflation. Assess for radial artery patency using the reverse Barbeau test. Place the pulse oximeter on the first or second finger of the affected arm. Occlude the ulnar artery to assess patency of the radial artery. Observe for waveforms on plethysmography. If no waveforms are seen on plethysmography when occluding the ulnar artery, the TR band should be slowly deflated

while holding pressure on the ulnar artery until the waveform returns (so-called patent hemostasis). Now the radial artery is patent. Maintain the wrist in a neutral position or with a small pillow underneath to ensure patient comfort. Perform periodic physical examinations while waiting to remove the TR band. This should include inspection for any signs of bleeding, edema, color of extremity, temperature, capillary refill, pain, and power. Prevent use of the affected extremity and maintain a neutral position.

When it is time to remove the TR band (30 minutes after diagnostic catheterization or 2 hours after the end of PCI or cessation of bivalirudin infusion), remove 1 to 2 cc of air and watch for any bleeding. If any signs of bleeding are observed, insert air until hemostasis is obtained and retry removing air in 5 to 10 minutes. If no bleeding is observed, 1 to 2 cc of air must be removed every 2 to 3 minutes until all the air is removed and hemostasis obtained. The TR band can now be removed, the site dressed with a sterile transparent dressing, and the site observed for any bleeding.

Postprocedure Care

Patients should have radial artery patency assessed before discharge and during the first postprocedure visit. Patients should be instructed not to manipulate the wrist for 24 hours after the procedure and to not lift any objects heavier than 3 to 5 lb for the next 2 days. The following

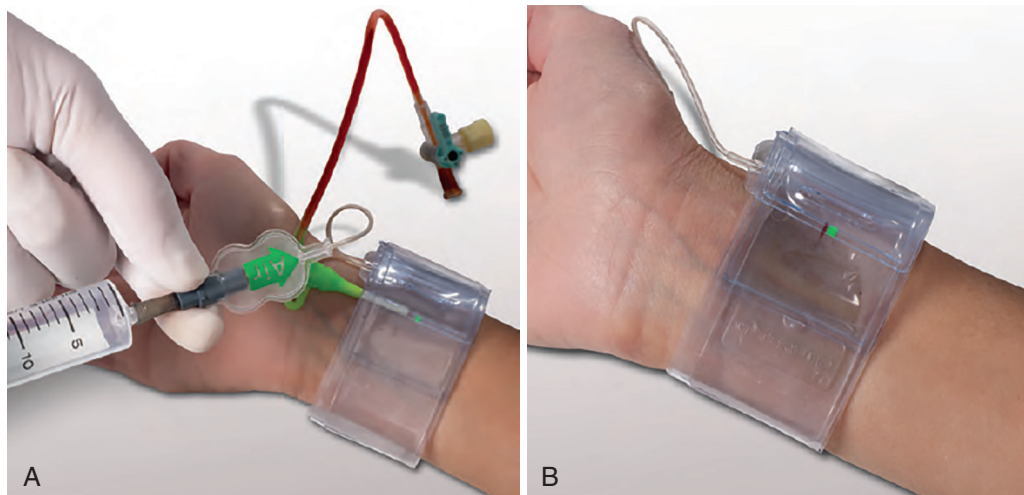


FIGURE 3.28 Transradial access site closure using a TR band (Terumo). **A**, The radial sheath is pulled back by 2 to 3 cm, and the TR band is applied such that the green marker is over the arteriotomy site (not the skin puncture site). The balloon is injected into the port (maximum of 18 cc). **B**, The sheath is removed and air is removed from the balloon until a flash of blood is seen, at which point 1 to 2 cc of air is reinjected until hemostasis is obtained. (Reprinted with permission from Terumo™, © 2014. All rights reserved.)

discharge instructions may be appropriate, although this is not driven by evidence, and variations based on local practice are common:

- Protect your wrist from bending for 48 hours. Deep bending of your wrist could cause bleeding.
- Do not lift, push, or pull anything over 5 lb for 48 hours and over 10 lb for 1 week.
- Do not write or type for 48 hours.
- Do not use your hand or arm to support your weight when rising from a chair or bed for 48 hours.
- Do not drive a car for 48 hours unless instructed by your doctor. Someone else should drive you home.
- Do not operate a lawnmower, motorcycle, chainsaw, or all-terrain vehicle for 48 hours.
- Do not soak the arm or swimming for 1 week. Showering is fine.
- All activities are permitted after 1 week if no problems occur.
- Call your doctor for any bleeding, swelling, or pain at the site.

Complications and Challenges

Radial Artery Occlusion

A relatively common complication of radial access is early and late radial artery occlusion, virtually all of which is asymptomatic, and the majority will spontaneously recanalize within 1 month. The incidence is variable from 1.1% to 20% and depends on the patient population and diagnostic test adopted. Risk factors for radial artery occlusion include large sheath size (sheath-to-artery ratio), occlusive hemostasis, and lack of anticoagulation use. Other risk factors for radial artery occlusion such as longer sheath and nonhydrophilic coating are controversial.⁹⁵ Asymptomatic radial artery occlusion can be detected by plethysmography or color Doppler ultrasonography. Symptomatic patients present with signs and symptoms of arterial insufficiency—the five Ps (pain, paresthesia, paralysis, pallor, and pulselessness)—which is extremely

rare given dual blood supply to the hand.⁹⁶ Radial artery occlusion, even if asymptomatic, can limit future radial access and limit the use of the radial artery for dialysis fistula as a conduit for bypass grafts or invasive arterial pressure monitoring and hence should be prevented when possible. The incidence of radial artery occlusion can be minimized by using smaller sheath sizes less than the radial artery diameter, using anticoagulation, avoiding repeated access of the radial artery, and using patent hemostasis after sheath removal.^{94,97} Other measures that may potentially reduce the risk of radial artery occlusion include use of hydrophilic sheaths, use of drugs to reduce radial artery spasm, and limiting the duration of radial artery compression.⁹⁴ Using these measures, the rate of radial artery occlusion is around 1.1% to 1.8%.⁹⁷ Treatment for asymptomatic patients is observation alone. If radial artery occlusion is noted early after the procedure (3–4 hours after removal of the TR band), ipsilateral ulnar artery compression for 1 hour to promote radial artery reopening has been shown to be successful.⁹⁸ In addition, treatment with anticoagulation (enoxaparin or fondaparinux) for 4 weeks increases the rate of recanalization.⁹⁹ Patients who are extremely symptomatic need revascularization either by percutaneous technique or by surgery, though this appears to be very rare.

Access Failure

Many studies have evaluated the predictors of radial access failure. Access failure for the transradial procedure can be a failure to cannulate the artery; failure to advance the catheter to the ascending aorta because of spasm, loops, or tortuosity; or failure to obtain adequate guide support, all of which necessitate conversion to alternate access routes (femoral, ulnar, or contralateral radial artery). A few patient-related factors such as advanced age, female, and short stature are associated with increased failure rates.¹⁰⁰

- *Radial artery spasm* (Figure 3.29): This can be prevented by adequate sedation before the procedure (even before

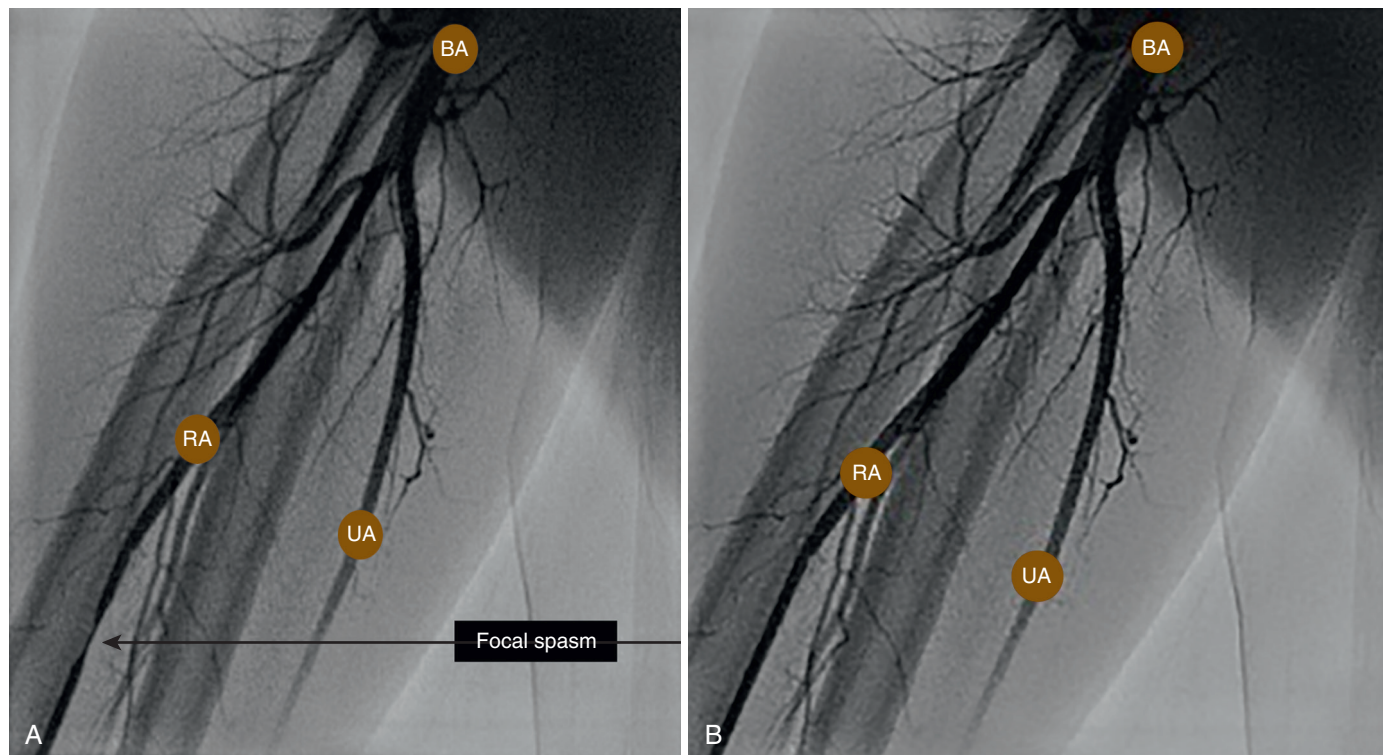


FIGURE 3.29 Radial artery spasm. **A**, Focal spasm seen just distal to the radial artery sheath (black arrow). **B**, Spasm relieved after administration of an intraarterial vasodilator cocktail. BA, Brachial artery; RA, radial artery; UA, ulnar artery. (Reproduced with permission from Patel T, Shah S, Rihal C, et al. *Patel's Atlas of Transradial Intervention: the basics and beyond*. Malvern, PA: HMP Communications LLC; 2012.)

the administration of a local anesthetic). This minimizes the circulating catecholamine-induced vasospasm. In addition, administering an intraarterial vasodilator cocktail after access is obtained can minimize spasm. Intraarterial verapamil or diltiazem with or without nitroglycerin is routinely used, although the cocktail has been variable. In addition, using smaller size sheaths with a hydrophilic coating and smaller sized catheters can minimize spasm.

- **Radial loops (Figure 3.30):** These are a common arterial anomaly that can be an obstacle for advancement of wires and catheters and increase the risk of radial artery spasm and perforation. Most radial loops can be traversed with a guidewire (preferably a hydrophilic wire) or by using a 0.014-inch coronary wire. Balloon-assisted tracking involves use of a coronary balloon that is nominally inflated to assist passage of a guide catheter over a 0.014-inch wire by creating a smoother transition from catheter tip to wire. After the catheter is passed beyond the loop, the loops usually straighten. In rare cases, switching over to a different access may be required.
- **Subclavian or brachiocephalic artery tortuosity (Figure 3.31):** Increased subclavian or brachiocephalic artery tortuosity caused by unwinding of the aorta is commonly seen in older adults and in those with hypertension. Common maneuvers to help navigate this include asking patients to take a deep breath to straighten the segment or to use an angled hydrophilic guidewire. Switching to a left radial approach can be considered. Additional considerations include use of a long hydrophilic sheath (e.g., R2P destination slender 75 cm/85 cm or 95 cm)



FIGURE 3.30 Radial artery loop and tortuosity. (Courtesy of Dr. Sudhanva Hegde, Kings County Medical Center, New York.)

after the tortuosity is navigated to assist with PCI because the sheath tip will be stationed in the ascending aorta.

- **Lack of guide support (Figure 3.32):** Switching the guide based on the need and considering specific transradial guide catheters can help because they have secondary

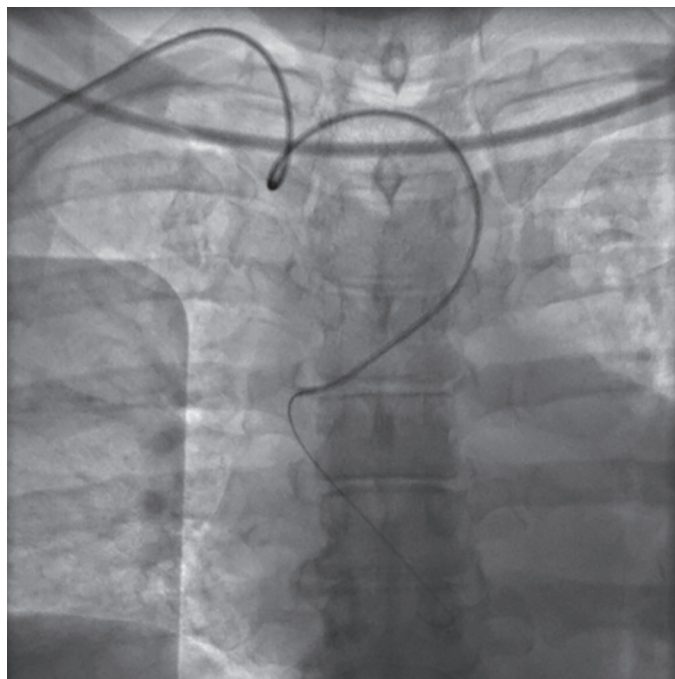


FIGURE 3.31 Subclavian and brachiocephalic artery tortuosity. (Courtesy of Dr. Sudhanva Hegde, Kings County Medical Center, New York.)

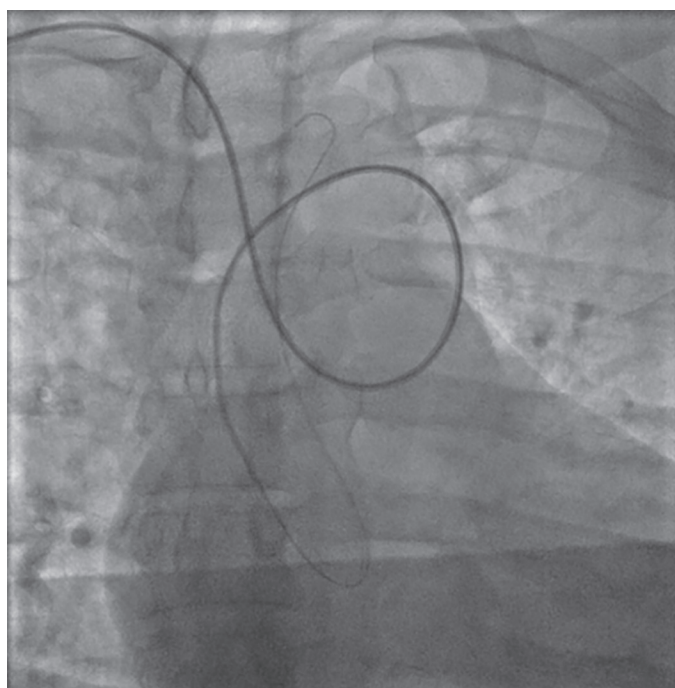


FIGURE 3.32 Low insertion of the brachiocephalic artery into the descending aorta. (Courtesy of Dr. Sudhanva Hegde, Kings County Medical Center, New York.)

curves that use the contralateral aortic wall for support. In addition, sheathless guide catheters that allow a larger inner diameter catheter without increasing the outer diameter have been developed to provide more support.¹⁰¹ Not fully inserting the introducer sheath (which has a larger outer diameter than the guide catheter) into the radial artery may also allow use of larger size guides without causing radial artery spasm. Switching to the left radial approach can also be considered.

Perforation

Perforation of the radial artery is usually caused by forceful manipulation of the hydrophilic wire, sheath, or catheter. The incidence is around 1%. The site of perforation can be along the course of the artery. However, common sites are the forearm and the arm. Risk factors include radial loops and tortuosities. Diagnosis is on angiography demonstrating contrast extravasation. Failure to achieve hemostasis can lead to hematoma formation or compartment syndrome in the forearm. If perforation is detected at the time of guide catheter advancement, the catheter should be advanced across the site of the perforation and the coronary procedure carried out. The guide serves as an internal hemostasis to prevent contrast extravasations even in fully anticoagulated patients. At the end of the coronary procedure, the guide should be withdrawn over a wire just distal to the site of perforation and repeat angiography performed to evaluate for the perforation (Figure 3.33). Most perforations can be sealed with this technique. Application of the blood pressure cuff to the forearm for external compression with inflation to 30 to 50 mm Hg may also be helpful. Treatment of patients with hematoma and compartment syndrome is described next.

Hematoma

The incidence of hematoma is 14.4%.¹⁰² Hematoma may occur at the site of the sheath insertion or along the course of the artery—forearm, arm, and even infraclavicular. Hematoma at the sheath insertion site is usually caused by ineffective compression. Forearm hematoma is caused by radial artery perforation during the introduction of the wire, sheath, or catheter. Most small hematomas are asymptomatic. Larger hematoma can cause symptoms of hand ischemia, especially when collateral circulation of the hand is poor. Treatment is by manual compression and reversal of anticoagulation if required. Effective compression of the forearm can be achieved by using a blood pressure cuff, though such nonspecific compression may sometimes facilitate development of compartment syndrome. Treatment of patients with compartment syndrome is described next.

Compartment Syndrome

This is a very rare complication with a reported incidence of 0.1% to 0.4%.¹⁰³ This is caused by radial artery perforation in the forearm. The forearm has the anterior compartment, which contains muscles and neurovascular bundles covered by the antebrachial fascia (deep fascia of the forearm). As such, any bleeding contained within the fascia can cause high fluid pressure (which prevents venous and lymphatic drainage with edema), nerve damage, and eventually muscle damage collectively called compartment syndrome. Patients present with symptoms and signs of ischemia with the five Ps—pain, paresthesia, paralysis, pallor, and pulselessness. Pain is usually out of proportion to the injury, especially with passive extension of the fingers (pathognomonic sign). Radial and ulnar pulses are usually intact. Treatment is by urgent surgery (extensive fasciotomy). Late consequences include limb ischemia, hand paralysis, septicemia, and death.

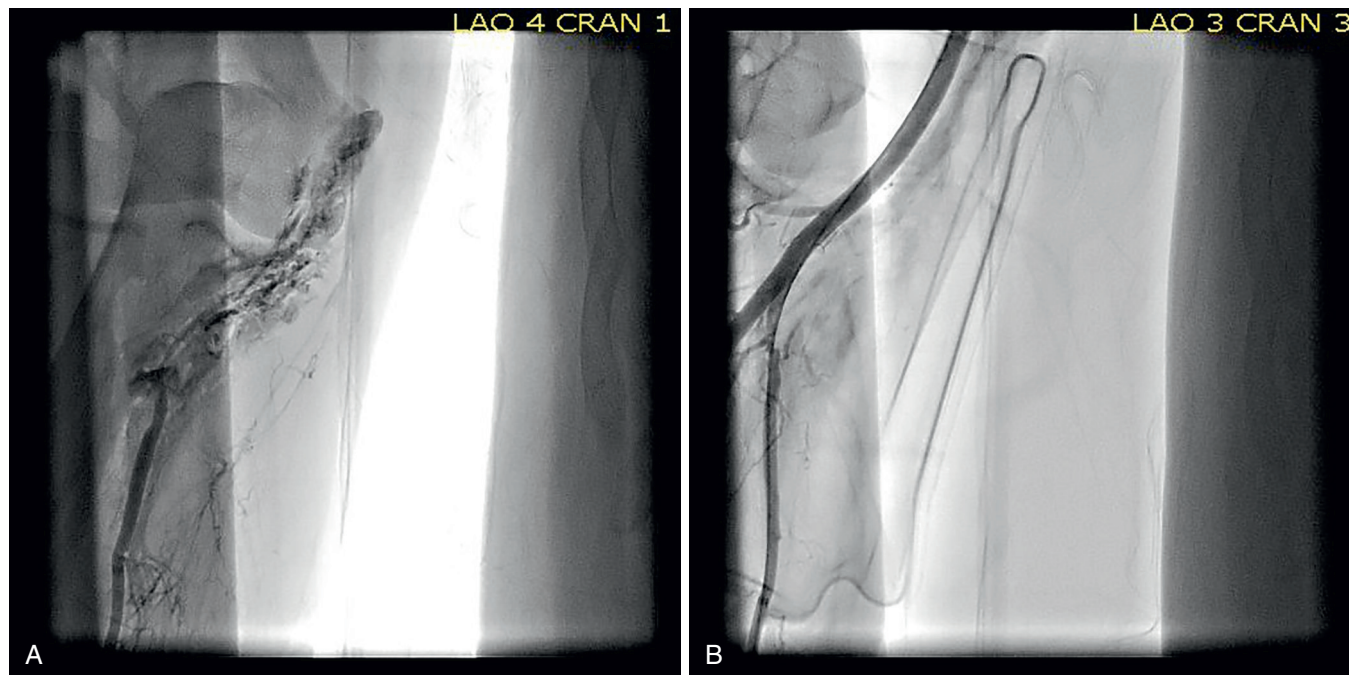


FIGURE 3.33 Radial artery perforation. **A**, Guidewire-induced radial artery perforation at the beginning of the procedure in a patient presenting with ST-segment elevation myocardial infarction. The true lumen was wired, a guide catheter was passed over it, and percutaneous coronary intervention was performed on the culprit artery. **B**, Perforation site at the end of the procedure showing no active extravasation of contrast.

Radial Artery Pseudoaneurysm

Similar to femoral artery pseudoaneurysm, radial artery pseudoaneurysm (Figure 3.34) is caused by ineffective hemostasis resulting in an aneurysmal dilation lined by fibrous tissue and thrombus with communication with the artery via a tract. The incidence is about 0.1%.¹⁰³ Risk factors for pseudoaneurysm include multiple puncture attempts, aggressive anticoagulation therapy, use of large sheaths, and ineffective manual compression.¹⁰³ Patients present with pain or swelling at the arterial puncture site. Diagnosis is by color Doppler ultrasonography. Treatment involves prolonged manual compression, cessation or reversal of anticoagulation as needed, ultrasound-guided compression or thrombin injection, and in rare cases surgery.

Radial Arteriovenous Fistula

Arteriovenous fistula between the radial artery and the veins is a rare complication (0.3%) occurring during cannulation of the artery.¹⁰⁴ Patients may present with pain and swelling and rarely with signs and symptoms of high-output cardiac failure. Examination reveals a palpable thrill or a bruit. Diagnosis is confirmed by color Doppler ultrasonography. Treatment is by prolonged manual compression. If this fails, surgery or use of covered stents may be considered.

Sterile Granuloma

Sterile granuloma at the entry site is caused by chronic inflammation at the arterial entry site from hydrophilic-coated sheaths (incidence up to 2% with certain older brands of sheath).¹⁰⁵ Patients present 2 to 3 weeks after the procedure with swelling. There are usually no systemic signs of fever or increased white blood cell count. The

differential diagnosis includes infection or pseudoaneurysm. Ultrasonography should be performed to rule out pseudoaneurysm. Diagnosis is by biopsy that shows sterile granulomas with chronic inflammation and giant cell reaction. Treatment involves surgical drainage.

Radial Artery Avulsion

This is a rare complication caused by excessive radial artery spasm during sheath removal.¹⁰⁶ In cases of excessive spasm, treatment should include intraarterial vasodilators, use of sedation, and slow retraction of the sheath over extended periods of time. In some cases, the sheath should be left in place, and an attempt at removal should be performed several hours later. In very rare cases, general anesthesia may be necessary to completely resolve the spasm.

ULNAR ARTERIAL ACCESS AND CLOSURE

The ulnar artery can be used as an alternative to the radial artery for percutaneous coronary and peripheral vascular procedures. The artery is usually smaller than the radial artery (although this is variable); has a deeper course in the forearm and wrist, making it difficult to palpate; and lies in close proximity to the neurovascular bundle at the wrist. Preprocedural considerations, access technique, and postprocedure care, including closure, are similar to those described for radial access. Transulnar access has been found to have a higher crossover rate caused by access failure when compared with transradial access. However, in a few patient subsets, the ulnar artery pulse may be stronger than the radial and can serve as an access site for failed transradial access.

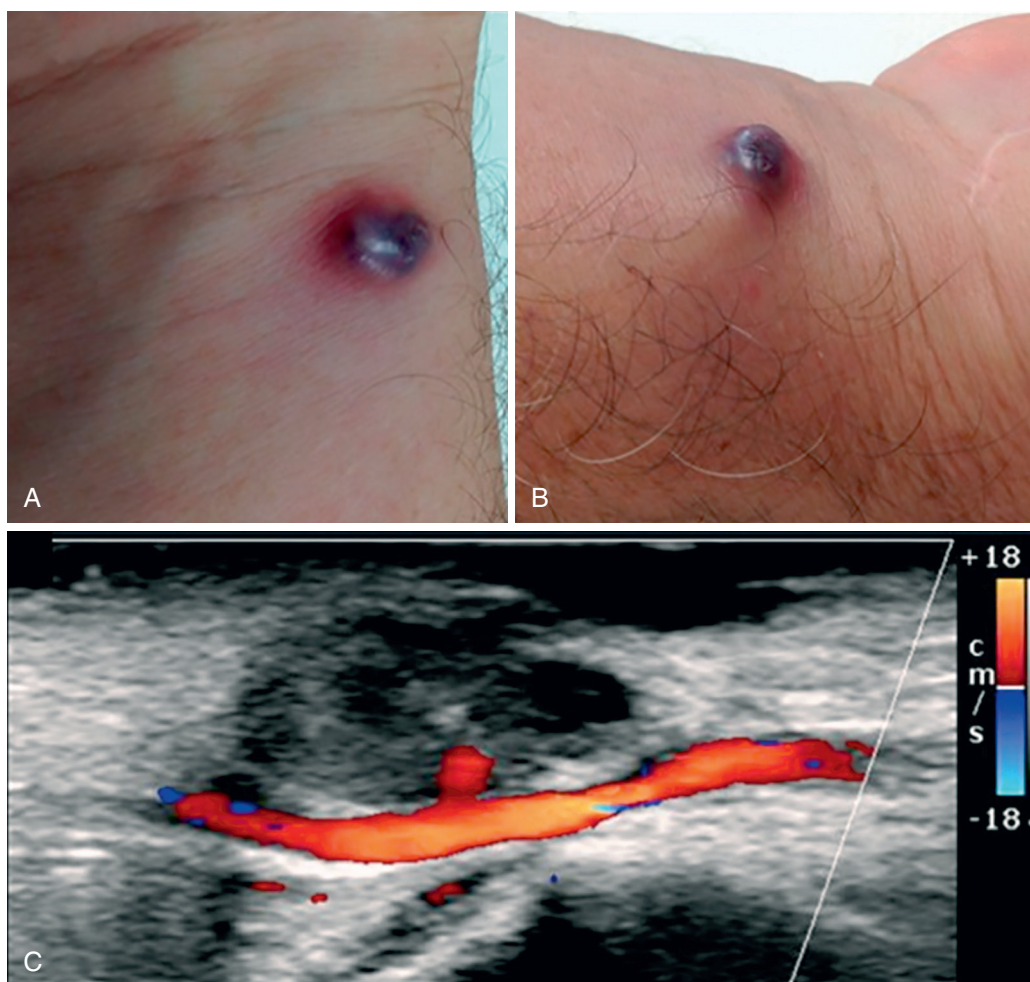


FIGURE 3.34 Late development of radial artery pseudoaneurysm. **A** and **B**, Swelling at the radial artery puncture site 5 months after the transradial procedure. **C**, Duplex ultrasound image of the radial artery showing a large, patent vessel with a short neck of blood flow into a partially thrombosed pseudoaneurysmal sac. (Courtesy of Drs. Ravikiran Korabathina, Bayfront Health, St. Petersburg, Fla.; and John T. Coppola, New York University School of Medicine, New York.)

DISTAL RADIAL ARTERIAL ACCESS AND CLOSURE

Distal radial artery access in the anatomic snuff box is an emerging alternative for proximal radial artery access for coronary angiography and intervention, especially with the left radial approach.¹⁰⁷ The anatomic snuff box is a triangular space over the dorsum of the hand bordered by the tendon of the extensor pollicis longus muscle medially and by the tendons of the abductor pollicis longus and extensor pollicis brevis muscles laterally. The radial artery lies superficially in this triangular space over a bony floor and hence is easy to palpate for access and compress for hemostasis. The artery is accessed in this snuff box (or just distal to it), typically with an anterior puncture technique under ultrasound guidance. The advantages of the technique include (1) patient comfort because there is no requirement to keep the hand supinated (especially in patients with orthopedic issues such as a frozen shoulder or elbow); (2) a decreased incidence of proximal radial artery occlusion, thus preserving the artery for future use as a bypass conduit or for AVF access; and (3) operator comfort and reduced radiation exposure during left radial approach because the arm can be crossed across the

midline, mimicking a right femoral access position. The disadvantages include (1) smaller size of the artery compared with the proximal radial artery, (2) a steep learning curve, and (3) an inability to reach the coronaries with conventional length catheters in taller patients. Hemostasis can be obtained using dedicated devices such as the SafeGuard or PreludeSync Distal device.

BRACHIAL ARTERIAL ACCESS AND CLOSURE

Introduction and Anatomy

With the increase in transradial procedures, brachial artery access is less preferred because it has a higher complication profile. The advantage of brachial access over radial access is the larger size of the artery, which can accommodate larger sheath sizes. However, brachial access carries with it the risk of distal ischemia and embolization. The brachial artery is a continuation of the axillary artery below the lower border of the teres major muscle, runs down the ventral surface of the arm into the cubital fossa on the medial aspects of the biceps brachialis, and divides into the radial and ulnar arteries. The artery is in close proximity to the median nerve, which is medial to the

artery at the level of the cubital fossa. In addition, a fascia covers the brachial artery, and hence a hematoma can risk compartment syndrome.

Procedure

The arm is abducted on an arm board, and the brachial artery site in and around the antecubital fossa is prepped and draped. Preprocedural considerations are similar to those described in the radial access section. The artery is palpated just proximal to the antecubital fossa where the biceps tendon can be felt. A 21-gauge micropuncture kit is preferred to minimize complications. The artery is entered with the modified Seldinger technique and exchanged for a suitable size of sheath. Anterior wall puncture is preferable to a through-and-through puncture to reduce the risk of hematoma. Brachial artery access can also be performed under ultrasound guidance. After access is obtained, intraarterial administration of a vasodilator cocktail will help minimize spasm. Anticoagulation with heparin (or bivalirudin for patients with heparin-induced thrombocytopenia) also can potentially reduce the risk of ischemic complications.

Closure and Complications

After the procedure, the sheath should be left in for a short period of time and removed immediately after diagnostic catheterization or after the effect of anticoagulants has worn off after interventional procedures (as described in the femoral arterial access section). The most commonly used technique is manual compression. The reported rates of complication are high, and many patients with access complication require surgical correction (for brachial artery thrombosis or pseudoaneurysm).¹⁰⁷ Topical hemostatic agents may be used as an adjunct to manual compression. In addition, various VCDs such as the Angio-Seal have been used for brachial artery hemostasis with a high success rate.¹⁰⁸ However, complications such as brachial artery occlusion and pseudoaneurysm can occur.¹⁰⁸

VENOUS ACCESS AND CLOSURE

Right Heart Catheterization via the Basilic Vein

Anatomy

The basilic vein arises from the dorsum of the hand, traverses through the medial part of the forearm and arm, and continues as the axillary vein and the subclavian vein, which joins with the internal jugular vein to form the brachiocephalic vein, which drains into the superior vena cava (SVC) and then into the right atrium. The basilic vein at the elbow is being increasingly used for right heart catheterization.

Procedure

Have the nurse insert an intravenous heparin lock in the basilic vein in the prep area. Usually an 18- or 20-gauge line should be placed. Exchange the line for a 5-Fr sheath in the cardiac catheterization laboratory after prepping and draping the area. A 5-Fr Swan-Ganz catheter is now advanced while

injecting saline through it into the axillary and subclavian vein into the brachiocephalic vein, SVC, and the right atrium. In some patients, the subclavian vein joins the internal jugular vein into the brachiocephalic vein at an angle that may make the passage of the Swan-Ganz catheter difficult. In such cases a 0.021- or 0.025-inch Swan wire or a 0.014- or 0.018-inch coronary guidewire can be used and the catheter advanced over this wire.

Complication

In rare cases, perforation of the vein, especially at the point of insertion into the internal subclavian vein, can result in infraclavicular hematoma.

Other Venous Access—Femoral, Internal Jugular, and Brachial

Procedure

Central venous access via the femoral vein, the internal jugular vein, or the brachial vein using ultrasound guidance is gaining popularity. Under sterile conditions, the area is prepped and draped. Ultrasonography is then performed to locate the vein. The vein is distinguished from the artery because it is more compressible than the artery and with the triphasic Doppler signal from the artery. When the ideal site is obtained, local anesthesia should be administered starting with the skin and working deeper (can be done under ultrasound guidance). An 18- or 21-gauge needle is then used to enter the vein under direct ultrasound guidance, and the modified Seldinger technique is used.

Closure

Manual compression is the most commonly used modality to obtain hemostasis after cannulation of the veins. However, VCDs such as the Perclose can be used to close larger veins such as the femoral vein (not a Food and Drug Administration–approved indication). Care must be taken not to pull back on the device too much because the thin-walled veins can tear. This is ideal for fully anticoagulated patients and those who receive thrombolytic agents. In addition, in patients undergoing structural heart procedure with the insertion of a sheath larger than 10-Fr size, preclosure of the vein using the technique described under the Perclose section has been found to be successful with a very low complication rate.¹⁰⁹ Most large-bore venous access sites can be closed using a purse-string or mattress suture.

Complications

Common complications include bleeding or hematoma at the site. Other complications include AVF formation.

CONCLUSIONS

Vascular access remains the key initial step of most procedures in the interventional suite. Careful planning is necessary to choose the optimal access site, though for arterial access, the radial artery is gaining popularity. Nevertheless, femoral arterial access will remain important for procedures that need larger diameter access sites, such as for

percutaneous valves or hemodynamic support devices. Hemostasis is also a critical part of the procedure, and this stage is crucial to minimize what has become the most common source of complications in patients undergoing interventional procedures—vascular complications.

Visit Elsevier eBooks+ to access the complete list of references.

SELECTED REFERENCES

- Babu SC, Piccorelli GO, Shah PM, et al. Incidence and results of arterial complications among 16,350 patients undergoing cardiac catheterization. *J Vasc Surg*. 1989;10(2):113-116.
- Feldman DN, Swaminathan RV, Kaltenbach LA, et al. Adoption of radial access and comparison of outcomes to femoral access in percutaneous coronary intervention: an updated report from the National Cardiovascular Data Registry (2007-2012). *Circulation*. 2013;127(23):2295-2306.
- Rupp SB, Vogelzang RL, Nemcek AA Jr, et al. Relationship of the inguinal ligament to pelvic radiographic landmarks: anatomic correlation and its role in femoral arteriography. *J Vasc Interv Radiol*. 1993;4(3):409-413.
- Turi ZG. Overview of vascular closure. In: *Endovascular Today*. Bryn Mawr Communications; 2009:24-32.
- Blank R, Rupprecht HJ, Schorrlepp M, et al. [Clinical value of Doppler ultrasound controlled puncture of the inguinal vessels with the "Smart Needle" within the scope of heart catheter examination]. *Z Kardiol*. 1997;86(8):608-614.
- Sorrentino S, Nguyen P, Salerno N, et al. Standard versus ultrasound-guided cannulation of the femoral artery in patients undergoing invasive procedures: a meta-analysis of randomized controlled trials. *J Clin Med*. 2020;9:677.
- Bangalore S, Barsness GW, Dangas GD, et al. Evidence-Based Practices in the Cardiac Catheterization Laboratory: A Scientific Statement from the American Heart Association. *Circulation*. 2021;144(5):e107-e119.
- Doyle BJ, Ting HH, Bell MR, et al. Major femoral bleeding complications after percutaneous coronary intervention: incidence, predictors, and impact on long-term survival among 17,901 patients treated at the Mayo Clinic from 1994 to 2005. *JACC Cardiovasc Interv*. 2008;1(2):202-209.
- Applegate RJ, Sacrinty MT, Kutcher MA, et al. Trends in vascular complications after diagnostic cardiac catheterization and percutaneous coronary intervention via the femoral artery, 1998 to 2007. *JACC Cardiovasc Interv*. 2008;1(3):317-326.
- Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUTY Trial. *J Am Coll Cardiol*. 2007;49(12):1362-1368.
- Grossman PM, Gurm HS, McNamara R, et al. Percutaneous coronary intervention complications and guide catheter size: bigger is not better. *JACC Cardiovasc Interv*. 2009;2(7):636-644.
- Tavris DR, Wang Y, Jacobs S, et al. Bleeding and vascular complications at the femoral access site following percutaneous coronary intervention (PCI): an evaluation of hemostasis strategies. *J Invasive Cardiol*. 2012;24(7):328-334.
- Sohail MR, Khan AH, Holmes DR Jr, et al. Infectious complications of percutaneous vascular closure devices. *Mayo Clin Proc*. 2005;80(8):1011-1015.
- Dangas G, Mehran R, Kokolis S, et al. Vascular complications after percutaneous coronary interventions following hemostasis with manual compression versus arteriotomy closure devices. *J Am Coll Cardiol*. 2001;38(3):638-641.
- Koreny M, Riedmuller E, Nikfardjam M, et al. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis. *JAMA*. 2004;291(3):350-357.
- Gall S, Tarique A, Natarajan A, et al. Rapid ambulation after coronary angiography via femoral artery access: a prospective study of 1,000 patients. *J Invasive Cardiol*. 2006;18(3):106-108.
- Mlekusch W, Dick P, Haumer M, et al. Arterial puncture site management after percutaneous transluminal procedures using a hemostatic wound dressing (Clo-Sur P.A.D.) versus conventional manual compression: a randomized controlled trial. *J Endovasc Ther*. 2006;13(1):23-31.
- Applegate RJ, Sacrinty MT, Kutcher MA, et al. Propensity score analysis of vascular complications after diagnostic cardiac catheterization and percutaneous coronary intervention 1998-2003. *Catheter Cardiovasc Interv*. 2006;67(4):556-562.
- Arora N, Matheny ME, Sepke C, et al. A propensity analysis of the risk of vascular complications after cardiac catheterization procedures with the use of vascular closure devices. *Am Heart J*. 2007;153(4):606-611.
- Chevalier B, Lancelin B, Koning R, et al. Effect of a closure device on complication rates in high-local-risk patients: results of a randomized multicenter trial. *Catheter Cardiovasc Interv*. 2003;58(3):285-291.
- Vaitkus PT. A meta-analysis of percutaneous vascular closure devices after diagnostic catheterization and percutaneous coronary intervention. *J Invasive Cardiol*. 2004;16(5):243-246.
- Kussmaul WG III, Buchbinder M, Whitlow PL, et al. Rapid arterial hemostasis and decreased access site complications after cardiac catheterization and angioplasty: results of a randomized trial of a novel hemostatic device. *J Am Coll Cardiol*. 1995;25(7):1685-1692.
- Nasu K, Tsuchikane E, Sumitsui S. Clinical effectiveness of the Prostar XL suture-mediated percutaneous vascular closure device following PCI: results of the Perclose Accelerated Ambulation and Discharge (PARADISE) trial. *J Invasive Cardiol*. 2003;15(5):251-256.
- Baim DS, Knopf WD, Hinohara T, et al. Suture-mediated closure of the femoral access site after cardiac catheterization: results of the suture to ambulate and discharge (STAND I and STAND II) trials. *Am J Cardiol*. 2000;85(7):864-869.
- Vidi VD, Matheny ME, Govindarajulu US, et al. Vascular closure device failure in contemporary practice. *JACC Cardiovasc Interv*. 2012;5(8):837-844.
- Bangalore S, Arora N, Resnic FS. Vascular closure device failure: frequency and implications: a propensity-matched analysis. *Circ Cardiovasc Interv*. 2009;2(6):549-556.
- Bangalore S, Bhatt DL. Femoral arterial access and closure. *Circulation*. 2011;124(5):E147-E156.
- Turi ZG, Wortham DC, Sampognaro GC, et al. Use of a novel access technology for femoral artery catheterization: results of the RECITAL trial. *J Invasive Cardiol*. 2013;25(1):13-18.
- Bui QT, Kolansky DM, Bannan A, et al. "Double wire" Angio Seal closure technique after balloon aortic valvuloplasty. *Catheter Cardiovasc Interv*. 2010;75(4):488-492.
- Abdel-Wahab M, Hartung P, Dumpies O, et al., on behalf of the CHOICE-CLOSURE Investigators. Comparison of a pure plug-based versus a primary suture-based vascular closure device strategy for transfemoral transcatheter aortic valve replacement: the CHOICE-CLOSURE Randomized Clinical Trial. *Circulation*. 2022;145(3):170-183.
- Martin JL, Pratsos A, Magargee E, et al. A randomized trial comparing compression, Perclose Proglide and Angio-Seal VIP for arterial closure following percutaneous coronary intervention: the CAP trial. *Catheter Cardiovasc Interv*. 2008;71(1):1-5.
- Bangalore S, Vidi VD, Liu CB, et al. Efficacy and safety of the nitinol clip-based vascular closure device (Starclose) for closure of common femoral arterial cannulation at or near the bifurcation: a propensity score-adjusted analysis. *J Invasive Cardiol*. 2011;23(5):194-199.
- Kiemeneij F, Laarmen GJ, Odekerken D, et al. A randomized comparison of percutaneous transluminal coronary angioplasty by the radial, brachial and femoral approaches: the access study. *J Am Coll Cardiol*. 1997;29(6):1269-1275.
- Bertrand OF, Rao SV, Pancholy S, et al. Transradial approach for coronary angiography and interventions: results of the first international transradial practice survey. *JACC Cardiovasc Interv*. 2010;3(10):1022-1031.
- Jolly SS, Amlani S, Hamon M, et al. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. *Am Heart J*. 2009;157(1):132-140.
- Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet*. 2011;377(9775):1409-1420.
- Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol*. 2012;60(24):2481-2489.
- Jolly SS, Cairns J, Niemela K, et al. Effect of radial versus femoral access on radiation dose and the importance of procedural volume: a substudy of the multicenter randomized RIVAL trial. *JACC Cardiovasc Interv*. 2013;6(3):258-266.
- Barbeau GR, Arsenault F, Dugas L, et al. Evaluation of the ulnopalmar arterial arches with pulse oximetry and plethysmography: comparison with the Allen's test in 1010 patients. *Am Heart J*. 2004;147(3):489-493.
- Stead SW, Stirt JA. Assessment of digital blood flow and palmar collateral circulation. Allen's test vs. photoplethysmography. *Int J Clin Monit Comput*. 1985;2(1):29-34.
- McGregor AD. The Allen test—an investigation of its accuracy by fluorescence angiography. *J Hand Surg*. 1987;12(1):82-85.
- Valgimigli M, Campo G, Penzo C, et al. Trans-radial coronary catheterization and intervention across the whole spectrum of Allen's test results. *J Am Coll Cardiol*. 2014;63(18):1833-1841.
- Hata M, Sezai A, Niino T, et al. Radial artery harvest using the sharp scissors method for patients with pathological findings on Allen's test. *Surg Today*. 2006;36(9):790-792.
- Mangano DT, Hickey RF. Ischemic injury following uncomplicated radial artery catheterization. *Anesth Analg*. 1979;58(1):55-57.
- Rao SV, Tremmel JA, Gilchrist IC, et al. Best practices for transradial angiography and intervention: a consensus statement from the Society for Cardiovascular Angiography and Intervention's transradial working group. *Catheter Cardiovasc Interv*. 2014;83(2):228-236.
- Pancholy S, Coppola J, Patel T, et al. Prevention of radial artery occlusion-patient hemostasis evaluation trial (PROPHET study): a randomized comparison of traditional versus patency documented hemostasis after transradial catheterization. *Catheter Cardiovasc Interv*. 2008;72(3):335-340.
- Bernat I, Bertrand OF, Rokyta R, et al. Efficacy and safety of transient ulnar artery compression to recanalize acute radial artery occlusion after transradial catheterization. *Am J Cardiol*. 2011;107(11):1698-1701.
- Zankl AR, Andrassy M, Volz C, et al. Radial artery thrombosis following transradial coronary angiography: incidence and rationale for treatment of symptomatic patients with low-molecular-weight heparins. *Clin Res Cardiol*. 2010;99(12):841-847.
- Scheer B, Perel A, Pfeiffer UJ. Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. *Crit Care*. 2002;6(3):199-204.
- Tizon-Marcos H, Barbeau GR. Incidence of compartment syndrome of the arm in a large series of transradial approach for coronary procedures. *J Interv Cardiol*. 2008;21(5):380-384.

REFERENCES

- Babu SC, Piccorelli GO, Shah PM, et al. Incidence and results of arterial complications among 16,350 patients undergoing cardiac catheterization. *J Vasc Surg*. 1989;10(2):113-116.
- Feldman DN, Swaminathan RV, Kaltenbach LA, et al. Adoption of radial access and comparison of outcomes to femoral access in percutaneous coronary intervention: an updated report from the National Cardiovascular Data Registry (2007-2012). *Circulation*. 2013;127(23):2295-2306.
- Rapoport S, Sniderman K, Morse S, et al. Pseudoaneurysm: a complication of faulty technique in femoral arterial puncture. *Radiology*. 1985;154(2):529-530.
- Rupp SB, Vogelzang RL, Nemcek AA Jr, et al. Relationship of the inguinal ligament to pelvic radiographic landmarks: anatomic correlation and its role in femoral arteriography. *J Vasc Interv Radiol*. 1993;4(3):409-413.
- Ellis SG, Bhatt D, Kapadia S, et al. Correlates and outcomes of retroperitoneal hemorrhage complicating percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2006;67(4):541-545.
- Grier D, Hartnell G. Percutaneous femoral artery puncture: practice and anatomy. *Br J Radiol*. 1990;63(752):602-604.
- Turi ZG. Overview of vascular closure. In: *Endovascular Today*. Bryn Mawr Communications; 2009:24-32.
- Blank R, Rupprecht HJ, Schorrlepp M, et al. [Clinical value of Doppler ultrasound controlled puncture of the inguinal vessels with the "Smart Needle" within the scope of heart catheter examination]. *Z Kardiol*. 1997;86(8):608-614.
- Wacker F, Wolf KJ, Fobbe F. Percutaneous vascular access guided by color duplex sonography. *Eur Radiol*. 1997;7(9):1501-1504.
- Sorrentino S, Nguyen P, Salerno N, et al. Standard versus ultrasound-guided cannulation of the femoral artery in patients undergoing invasive procedures: a meta-analysis of randomized controlled trials. *J Clin Med*. 2020;9:677.
- Bangalore S, Barsness GW, Dangas GD, et al. Evidence-Based Practices in the Cardiac Catheterization Laboratory: A Scientific Statement from the American Heart Association. *Circulation*. 2021;144(5):e107-e119.
- Chhatriwalla AK, Bhatt DL. Walk this way: early ambulation after cardiac catheterization—good for the patient and the health care system. *Mayo Clin Proc*. 2006;81(12):1535-1536.
- Doyle BJ, Ting HH, Bell MR, et al. Major femoral bleeding complications after percutaneous coronary intervention: incidence, predictors, and impact on long-term survival among 17,901 patients treated at the Mayo Clinic from 1994 to 2005. *JACC Cardiovasc Interv*. 2008;1(2):202-209.
- Applegate RJ, Sacrinty MT, Kutcher MA, et al. Trends in vascular complications after diagnostic cardiac catheterization and percutaneous coronary intervention via the femoral artery, 1998 to 2007. *JACC Cardiovasc Interv*. 2008;1(3):317-326.
- Yatskar L, Selzer F, Feit F, et al. Access site hematoma requiring blood transfusion predicts mortality in patients undergoing percutaneous coronary intervention: data from the National Heart, Lung, and Blood Institute Dynamic Registry. *Catheter Cardiovasc Interv*. 2007;69(7):961-966.
- Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUTY Trial. *J Am Coll Cardiol*. 2007;49(12):1362-1368.
- Akhter N, Milford-Beland S, Roe MT, et al. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am Heart J*. 2009;157(1):141-148.
- Kinnaird TD, Stabile E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. *Am J Cardiol*. 2003;92(8):930-935.
- Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2003;24(20):1815-1823.
- Grossman PM, Gurm HS, McNamara R, et al. Percutaneous coronary intervention complications and guide catheter size: bigger is not better. *JACC Cardiovasc Interv*. 2009;2(7):636-644.
- Turi ZG. An evidence-based approach to femoral arterial access and closure. *Rev Cardiovasc Med*. 2008;9(1):7-18.
- Exaire JE, Tcheng JE, Kereiakes DJ, et al. Closure devices and vascular complications among percutaneous coronary intervention patients receiving enoxaparin, glycoprotein IIb/IIIa inhibitors, and clopidogrel. *Catheter Cardiovasc Interv*. 2005;64(3):369-372.
- Nasser TK, Mohler ER III, Wilensky RL, et al. Peripheral vascular complications following coronary interventional procedures. *Clin Cardiol*. 1995;18(11):609-614.
- Tavris DR, Wang Y, Jacobs S, et al. Bleeding and vascular complications at the femoral access site following percutaneous coronary intervention (PCI): an evaluation of hemostasis strategies. *J Invasive Cardiol*. 2012;24(7):328-334.
- Tiroch KA, Arora N, Matheny ME, et al. Risk predictors of retroperitoneal hemorrhage following percutaneous coronary intervention. *Am J Cardiol*. 2008;102(11):1473-1476.
- Farouque HM, Tremmel JA, Raissi Shabari F, et al. Risk factors for the development of retroperitoneal hematoma after percutaneous coronary intervention in the era of glycoprotein IIb/IIIa inhibitors and vascular closure devices. *J Am Coll Cardiol*. 2005;45(3):363-368.
- Derham C, Davies JF, Shahbazi R, et al. Iatrogenic limb ischemia caused by angiography closure devices. *Vasc Endovascular Surg*. 2006-2007;40(6):492-494.
- Sohail MR, Khan AH, Holmes DR Jr, et al. Infectious complications of percutaneous vascular closure devices. *Mayo Clin Proc*. 2005;80(8):1011-1015.
- Dangas G, Mehran R, Kokolis S, et al. Vascular complications after percutaneous coronary interventions following hemostasis with manual compression versus arteriotomy closure devices. *J Am Coll Cardiol*. 2001;38(3):638-641.
- Koreny M, Riedmuller E, Nikfardjam M, et al. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis. *JAMA*. 2004;291(3):350-357.
- Nikolsky E, Mehran R, Halkin A, et al. Vascular complications associated with arteriotomy closure devices in patients undergoing percutaneous coronary procedures: a meta-analysis. *J Am Coll Cardiol*. 2004;44(6):1200-1209.
- Doyle BJ, Konz BA, Lennon RJ, et al. Ambulation 1 hour after diagnostic cardiac catheterization: a prospective study of 1009 procedures. *Mayo Clin Proc*. 2006;81(12):1537-1540.
- Gall S, Tarique A, Natarajan A, et al. Rapid ambulation after coronary angiography via femoral artery access: a prospective study of 1,000 patients. *J Invasive Cardiol*. 2006;18(3):106-108.
- Chhatriwalla AK, Bhatt DL. You can't keep a good man (or woman) down. *J Invasive Cardiol*. 2006;18(3):109-110.
- Nguyen N, Hasan S, Caufield L, et al. Randomized controlled trial of topical hemostasis pad use for achieving vascular hemostasis following percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2007;69(6):801-807.
- Mlekusch W, Dick P, Haumer M, et al. Arterial puncture site management after percutaneous transluminal procedures using a hemostatic wound dressing (Clo-Sur P.A.D.) versus conventional manual compression: a randomized controlled trial. *J Endovasc Ther*. 2006;13(1):23-31.
- Balzer JO, Schwarz W, Thalhammer A, et al. Postinterventional percutaneous closure of femoral artery access sites using the Clo-Sur PAD device: initial findings. *Eur Radiol*. 2007;17(3):693-700.
- Brown DB. Current status of suture-mediated closure: what is the cost of comfort? *J Vasc Interv Radiol*. 2003;14(6):677-681.
- Cura FA, Kapadia SR, L'Allier PL, et al. Safety of femoral closure devices after percutaneous coronary interventions in the era of glycoprotein IIb/IIIa platelet blockade. *Am J Cardiol*. 2000;86(7):780-782, A789.
- Kahn ZM, Kumar M, Hollander G, et al. Safety and efficacy of the Perclose suture-mediated closure device after diagnostic and interventional catheterizations in a large consecutive population. *Catheter Cardiovasc Interv*. 2002;55(1):8-13.
- Wagner SC, Gonsalves CF, Eschelman DJ, et al. Complications of a percutaneous suture-mediated closure device versus manual compression for arteriotomy closure: a case-controlled study. *J Vasc Interv Radiol*. 2003;14(6):735-741.
- Applegate RJ, Sacrinty MT, Kutcher MA, et al. Propensity score analysis of vascular complications after diagnostic cardiac catheterization and percutaneous coronary intervention 1998-2003. *Catheter Cardiovasc Interv*. 2006;67(4):556-562.
- Arora N, Matheny ME, Sepke C, et al. A propensity analysis of the risk of vascular complications after cardiac catheterization procedures with the use of vascular closure devices. *Am Heart J*. 2007;153(4):606-611.
- Tavris DR, Gallauresi BA, Lin B, et al. Risk of local adverse events following cardiac catheterization by hemostasis device use and gender. *J Invasive Cardiol*. 2004;16(9):459-464.
- Chevalier B, Lancelin B, Koning R, et al. Effect of a closure device on complication rates in high-local-risk patients: results of a randomized multicenter trial. *Catheter Cardiovasc Interv*. 2003;58(3):285-291.
- Vaitkus PT. A meta-analysis of percutaneous vascular closure devices after diagnostic catheterization and percutaneous coronary intervention. *J Invasive Cardiol*. 2004;16(5):243-246.
- Gerckens U, Cattelans N, Lampe EG, et al. Management of arterial puncture site after catheterization procedures: evaluating a suture-mediated closure device. *Am J Cardiol*. 1999;83(12):1658-1663.
- Kussmaul WG III, Buchbinder M, Whitlow PL, et al. Rapid arterial hemostasis and decreased access site complications after cardiac catheterization and angioplasty: results of a randomized trial of a novel hemostatic device. *J Am Coll Cardiol*. 1995;25(7):1685-1692.
- Nasu K, Tsuchikane E, Sumitsuiji S. Clinical effectiveness of the Prostar XL suture-mediated percutaneous vascular closure device following PCI: results of the Perclose Accelerated Ambulation and Discharge (PARADISE) trial. *J Invasive Cardiol*. 2003;15(5):251-256.
- Slaughter PM, Chetty R, Flintoft VF, et al. A single center randomized trial assessing use of a vascular hemostasis device vs. conventional manual compression following PTCA: what are the potential resource savings? *Cathet Cardiovasc Diagn*. 1995;34(3):210-214.
- Ward SR, Casale P, Raymond R, et al. Efficacy and safety of a hemostatic puncture closure device with early ambulation after coronary angiography. *Angio-Seal Investigators*. *Am J Cardiol*. 1998;81(5):569-572.
- Baim DS, Knopf WD, Hinohara T, et al. Suture-mediated closure of the femoral access site after cardiac catheterization: results of the suture to ambulate and discharge (STAND I and STAND II) trials. *Am J Cardiol*. 2000;85(7):864-869.
- Vidi VD, Matheny ME, Govindarajulu US, et al. Vascular closure device failure in contemporary practice. *JACC Cardiovasc Interv*. 2012;5(8):837-844.
- Bangalore S, Arora N, Resnic FS. Vascular closure device failure: frequency and implications: a propensity-matched analysis. *Circ Cardiovasc Interv*. 2009;2(6):549-556.



55. Bangalore S, Bhatt DL. Femoral arterial access and closure. *Circulation*. 2011;124(5):E147-E156.
56. Turi ZG, Wortham DC, Sampognaro GC, et al. Use of a novel access technology for femoral artery catheterization: results of the RECITAL trial. *J Invasive Cardiol*. 2013;25(1):13-18.
57. Applegate RJ, Grabarczyk MA, Little WC, et al. Vascular closure devices in patients treated with anticoagulation and IIb/IIIa receptor inhibitors during percutaneous revascularization. *J Am Coll Cardiol*. 2002;40(1):78-83.
58. Bui QT, Kolansky DM, Bannan A, et al. "Double wire" Angio Seal closure technique after balloon aortic valvuloplasty. *Catheter Cardiovasc Interv*. 2010;75(4):488-492.
59. Abdel-Wahab M, Hartung P, Dumpies O, et al., on behalf of the CHOICE-CLOSURE Investigators. Comparison of a Pure Plug-Based versus a Primary Suture-Based Vascular Closure Device Strategy for Transfemoral Transcatheter Aortic Valve Replacement: The CHOICE-CLOSURE Randomized Clinical Trial. *Circulation*. 2022;145(3):170-183.
60. Scheinert D, Sievert H, Turco MA, et al. The safety and efficacy of an extravascular, water-soluble sealant for vascular closure: initial clinical results for Mynx. *Catheter Cardiovasc Interv*. 2007;70(5):627-633.
61. Azmoon S, Pucillo AL, Aronow WS, et al. Vascular complications after percutaneous coronary intervention following hemostasis with the Mynx vascular closure device versus the Angio-Seal vascular closure device. *J Invasive Cardiol*. 2010;22(4):175-178.
62. Martin JL, Pratsos A, Magargee E, et al. A randomized trial comparing compression, Perclose Proglide and Angio-Seal VIP for arterial closure following percutaneous coronary intervention: the CAP trial. *Catheter Cardiovasc Interv*. 2008;71(1):1-5.
63. Cherr GS, Travis JA, Ligush J Jr, et al. Infection is an unusual but serious complication of a femoral artery catheterization site closure device. *Ann Vasc Surg*. 2001;15(5):567-570.
64. Jaffan AA, Prince EA, Hampson CO, et al. The preclose technique in percutaneous endovascular aortic repair: a systematic literature review and meta-analysis. *Cardiovasc Intervent Radiol*. 2013;36(3):567-577.
65. Lee WA, Brown MP, Nelson PR, et al. Total percutaneous access for endovascular aortic aneurysm repair ("Preclose" technique). *J Vasc Surg*. 2007;45(6):1095-1101.
66. Branzan D, Sixt S, Rastan A, et al. Safety and efficacy of the StarClose vascular closure system using 7-Fr and 8-Fr sheath sizes: a consecutive single-center analysis. *J Endovasc Ther*. 2009;16(4):475-482.
67. Bangalore S, Vidi VD, Liu CB, et al. Efficacy and safety of the nitinol clip-based vascular closure device (StarClose) for closure of common femoral arterial cannulation at or near the bifurcation: a propensity score-adjusted analysis. *J Invasive Cardiol*. 2011;23(5):194-199.
68. Campeau L. Percutaneous radial artery approach for coronary angiography. *Cathet Cardiovasc Diagn*. 1989;16(1):3-7.
69. Kiemeny F, Laarmann GJ, Odekerken D, et al. A randomized comparison of percutaneous transluminal coronary angioplasty by the radial, brachial and femoral approaches: the access study. *J Am Coll Cardiol*. 1997;29(6):1269-1275.
70. Bertrand OF, Rao SV, Pancholy S, et al. Transradial approach for coronary angiography and interventions: results of the first international transradial practice survey. *JACC Cardiovasc Interv*. 2010;3(10):1022-1031.
71. Sanghvi K, Kurian D, Coppola J. Transradial intervention of iliac and superficial femoral artery disease is feasible. *J Interv Cardiol*. 2008;21(5):385-387.
72. Patel T, Shah S, Ranjan A, et al. Contralateral transradial approach for carotid artery stenting: a feasibility study. *Catheter Cardiovasc Interv*. 2010;75(2):268-275.
73. Jolly SS, Amlani S, Hamon M, et al. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. *Am Heart J*. 2009;157(1):132-140.
74. Cooper CJ, El-Sheikh RA, Cohen DJ, et al. Effect of transradial access on quality of life and cost of cardiac catheterization: a randomized comparison. *Am Heart J*. 1999;138(3 Pt 1):430-436.
75. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet*. 2011;377(9775):1409-1420.
76. Chhatrwalla AK, Amin AP, Kennedy KF, et al. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA*. 2013;309(10):1022-1029.
77. Mehta SR, Jolly SS, Cairns J, et al. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. *J Am Coll Cardiol*. 2012;60(24):2490-2499.
78. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol*. 2012;60(24):2481-2489.
79. Mamas MA, Ratib K, Routledge H, et al. Influence of access site selection on PCI-related adverse events in patients with STEMI: meta-analysis of randomised controlled trials. *Heart*. 2012;98(4):303-311.
80. Shah B, Bangalore S, Feit F, et al. Radiation exposure during coronary angiography via transradial or transfemoral approaches when performed by experienced operators. *Am Heart J*. 2013;165(3):286-292.
81. Lange HW, von Boetticher H. Randomized comparison of operator radiation exposure during coronary angiography and intervention by radial or femoral approach. *Catheter Cardiovasc Interv*. 2006;67(1):12-16.
82. Looi JL, Cave A, El-Jack S. Learning curve in transradial coronary angiography. *Am J Cardiol*. 2011;108(8):1092-1095.
83. Sanmartin M, Cuevas D, Moxica J, et al. Transradial cardiac catheterization in patients with coronary bypass grafts: feasibility analysis and comparison with transfemoral approach. *Catheter Cardiovasc Interv*. 2006;67(4):580-584.
84. Jolly SS, Niemela K, Xavier D, et al. Design and rationale of the radial versus femoral access for coronary intervention (RIVAL) trial: a randomized comparison of radial versus femoral access for coronary angiography or intervention in patients with acute coronary syndromes. *Am Heart J*. 2011;161(2):254-260, e251-e254.
85. Jolly SS, Cairns J, Niemela K, et al. Effect of radial versus femoral access on radiation dose and the importance of procedural volume: a substudy of the multicenter randomized RIVAL trial. *JACC Cardiovasc Interv*. 2013;6(3):258-266.
86. Barbeau GR, Arsenault F, Dugas L, et al. Evaluation of the ulnopalmar arterial arches with pulse oximetry and plethysmography: comparison with the Allen's test in 1010 patients. *Am Heart J*. 2004;147(3):489-493.
87. Stead SW, Stirt JA. Assessment of digital blood flow and palmar collateral circulation. Allen's test vs. photoplethysmography. *Int J Clin Monit Comput*. 1985;2(1):29-34.
88. McGregor AD. The Allen test—an investigation of its accuracy by fluorescein angiography. *J Hand Surg*. 1987;12(1):82-85.
89. Valgimigli M, Campo G, Penzo C, et al. Trans-radial coronary catheterization and intervention across the whole spectrum of Allen's test results. *J Am Coll Cardiol*. 2014;63(18):1833-1841.
90. Hata M, Sezai A, Niino T, et al. Radial artery harvest using the sharp scissors method for patients with pathological findings on Allen's test. *Surg Today*. 2006;36(9):790-792.
91. Mangano DT, Hickey RF. Ischemic injury following uncomplicated radial artery catheterization. *Anesth Analg*. 1979;58(1):55-57.
92. Coppola J, Patel T, Kwan T, et al. Nitroglycerin, nitroprusside, or both, in preventing radial artery spasm during transradial artery catheterization. *J Invasive Cardiol*. 2006;18(4):155-158.
93. Plante S, Cantor WJ, Goldman L, et al. Comparison of bivalirudin versus heparin on radial artery occlusion after transradial catheterization. *Catheter Cardiovasc Interv*. 2010;76(5):654-658.
94. Rao SV, Tremmel JA, Gilchrist IC, et al. Best practices for transradial angiography and intervention: a consensus statement from the Society for Cardiovascular Angiography and Intervention's transradial working group. *Catheter Cardiovasc Interv*. 2014;83(2):228-236.
95. Rathore S, Stables RH, Pauriah M, et al. Impact of length and hydrophilic coating of the introducer sheath on radial artery spasm during transradial coronary intervention: a randomized study. *JACC Cardiovasc Interv*. 2010;3(5):475-483.
96. Rhyne D, Mann T. Hand ischemia resulting from a transradial intervention: successful management with radial artery angioplasty. *Catheter Cardiovasc Interv*. 2010;76(3):383-386.
97. Pancholy S, Coppola J, Patel T, et al. Prevention of radial artery occlusion-patent hemostasis evaluation trial (PROPHET study): a randomized comparison of traditional versus patency documented hemostasis after transradial catheterization. *Catheter Cardiovasc Interv*. 2008;72(3):335-340.
98. Bernat I, Bertrand OF, Rokyta R, et al. Efficacy and safety of transient ulnar artery compression to recanalize acute radial artery occlusion after transradial catheterization. *Am J Cardiol*. 2011;107(11):1698-1701.
99. Zankl AR, Andrassy M, Volz C, et al. Radial artery thrombosis following transradial coronary angiography: incidence and rationale for treatment of symptomatic patients with low-molecular-weight heparins. *Clin Res Cardiol*. 2010;99(12):841-847.
100. Dehghani P, Mohammad A, Bajaj R, et al. Mechanism and predictors of failed transradial approach for percutaneous coronary interventions. *JACC Cardiovasc Interv*. 2009;2(11):1057-1064.
101. Sciahbasi A, Mancone M, Cortese B, et al. Transradial percutaneous coronary interventions using sheathless guiding catheters: a multicenter registry. *J Interv Cardiol*. 2011;24(5):407-412.
102. Scheer B, Perel A, Pfeiffer UJ. Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. *Crit Care*. 2002;6(3):199-204.
103. Tizon-Marcos H, Barbeau GR. Incidence of compartment syndrome of the arm in a large series of transradial approach for coronary procedures. *J Interv Cardiol*. 2008;21(5):380-384.
104. Kwac MS, Yoon SJ, Oh SJ, et al. A rare case of radial arteriovenous fistula after coronary angiography. *Korean Circ J*. 2010;40(12):677-679.
105. Kozak M, Adams DR, Ioffreda MD, et al. Sterile inflammation associated with transradial catheterization and hydrophilic sheaths. *Catheter Cardiovasc Interv*. 2003;59(2):207-213.
106. Abu-Ful A, Benharroch D, Henkin Y. Extraction of the radial artery during transradial coronary angiography: an unusual complication. *J Invasive Cardiol*. 2003;15(6):351-352.
107. Svegli GA, Di Giorgio A, Gasparone A, Babunashvili A. Anatomic basis and physiological rationale of distal radial artery access for percutaneous coronary and endovascular procedures. *JACC Cardiovasc Interv*. 2018;11(20):2113-2119.
108. Lupattelli T, Clerissi J, Clerici G, et al. The efficacy and safety of closure of brachial access using the Angio-Seal closure device: experience with 161 interventions in diabetic patients with critical limb ischemia. *J Vasc Surg*. 2008;47(4):782-788.
109. Mahadevan VS, Jimeno S, Benson LN, et al. Pre-closure of femoral venous access sites used for large-sized sheath insertion with the Perclose device in adults undergoing cardiac intervention. *Heart*. 2008;94(5):571-572.



4 Pharmacotherapy In The Modern Interventional Suite

HANI JNEID

PATHOPHYSIOLOGY OF ARTERIAL THROMBOSIS, 56

ASPIRIN, 56

Aspirin Dosage, 58

ORAL P₂Y₁₂ RECEPTOR INHIBITORS, 59

Ticlopidine, 59

Clopidogrel, 61

Prasugrel, 62

Ticagrelor, 62

Duration of Therapy with Oral P₂Y₁₂ Receptor Inhibitors, 62

Choice of Oral P₂Y₁₂ Receptor Inhibitor Therapy, 63

Use of Oral P₂Y₁₂ Receptor Inhibitors with Fibrinolytic Therapy, 63

Timing of Discontinuation of Oral P₂Y₁₂ Receptor Inhibitor Therapy, 63

Antithrombotic Therapy in Patients Receiving Long-Term Anticoagulation, 63

Oral Glycoprotein IIb/IIIa Receptor Inhibitors, 64

INTRAVENOUS ANTIPLATELET DRUGS, 64

Intravenous Glycoprotein IIb/IIIa Receptor Inhibitors, 64

Timing of Administration of Glycoprotein IIb/IIIa Receptor Inhibitor, 66

Choice of Intravenous Glycoprotein IIb/IIIa Receptor Inhibitor, 66

Timing of Discontinuation of Glycoprotein IIb/IIIa Receptor Inhibitors, 66

Cangrelor, 66

INTRAVENOUS ANTICOAGULANT DRUGS, 66

Unfractionated Heparin, 66

Enoxaparin, 68

Bivalirudin, 68

Fondaparinux, 69

Other Parenteral Anticoagulants, 69

Duration of Anticoagulation Therapy After Percutaneous Coronary Intervention, 69

VASODILATORS AND ANTIHYPERTENSIVE DRUGS, 69

Hypertension Urgency or Emergency, 69

The No-Reflow Phenomenon, 70

Selective Vasodilators and Antihypertensive Medications, 70

VASOPRESSORS AND INOTROPIC DRUGS, 71

Hypotension, 71

Acute Heart Failure or Cardiogenic Shock, 72

Selective Vasopressors and Inotropes, 72

PROCEDURAL SEDATION: ANXIOLYTICS AND ANALGESICS, 74

MISCELLANEOUS DRUGS, 74

Antiarrhythmic Medications, 74

Diuretics, 74

CONCLUSIONS, 74

The major aims of pharmacotherapy during percutaneous coronary intervention (PCI) and invasive cardiac procedures are to avoid the adverse consequences related to iatrogenic plaque rupture during balloon angioplasty and stent deployment, to reduce the hazards of thrombus formation on the intracoronary (IC) PCI equipment, and to mitigate myocardial ischemia and all periprocedural complications. The informed, effective, and judicious use of drugs in the modern interventional suite allows invasive cardiovascular procedures to be performed safely while maintaining the hemodynamic and electrical stability of patients and minimizing complications.

PATHOPHYSIOLOGY OF ARTERIAL THROMBOSIS

Thrombosis is fundamental to the process of arterial injury associated with both acute coronary syndromes (ACSs) and PCIs. The pathogenesis of coronary arterial thrombosis is characterized by atherosclerotic plaque disruption (usually rupture or erosion) followed by platelet activation and aggregation and resultant thrombus formation. Irrespective of whether plaque disruption occurs spontaneously or as a result of mechanical disruption during coronary balloon angioplasty, platelets first adhere to the injured endothelium by binding to class I glycoproteins (GPs)¹ (Figure 4.1). Thrombin and other agonists, such as adenosine diphosphate (ADP) and epinephrine, activate the platelets and conformational changes in the GP IIb/IIIa receptor and platelet degranulation.¹ This results in the release of more

vasoactive substances such as serotonin, thromboxane A₂ (TXA₂), and more ADP, which are important mediators of thrombosis that stimulate further platelet activation and recruitment. Activation of the ADP-specific purinergic P₂Y₁₂ receptor results in activation of the GP IIb/IIIa receptor, granule release, amplification of platelet aggregation, and stabilization of the platelet aggregate.² TXA₂ is another key platelet agonist that is derived from arachidonic acid through conversion by cyclooxygenase-1 and thromboxane synthase.³ The binding of these agonists to their platelet receptors ultimately activates the GP IIb/IIIa receptor, which promotes the interaction of adjacent platelets through fibrinogen, forming cross-bridges between activated platelets and leading to platelet aggregation (Figure 4.2).

The platelet clot is stabilized by fibrin derived from the coagulation cascade⁴ (Figure 4.3). Initiation of blood coagulation occurs mainly through tissue factor (TF), a membrane GP that becomes exposed to blood after plaque disruption. Thrombin is another potent platelet agonist that activates platelet by binding protease-activated receptor on the platelet surface.⁵ Thrombin-mediated cleavage of fibrinogen into fibrin is even more important for hemostasis than thrombin-mediated platelet activation.⁵

ASPIRIN

When aspirin was marketed in 1899 for its efficacy in relieving rheumatologic conditions, its manufacturer issued a reassurance for the public that it had no harmful effects

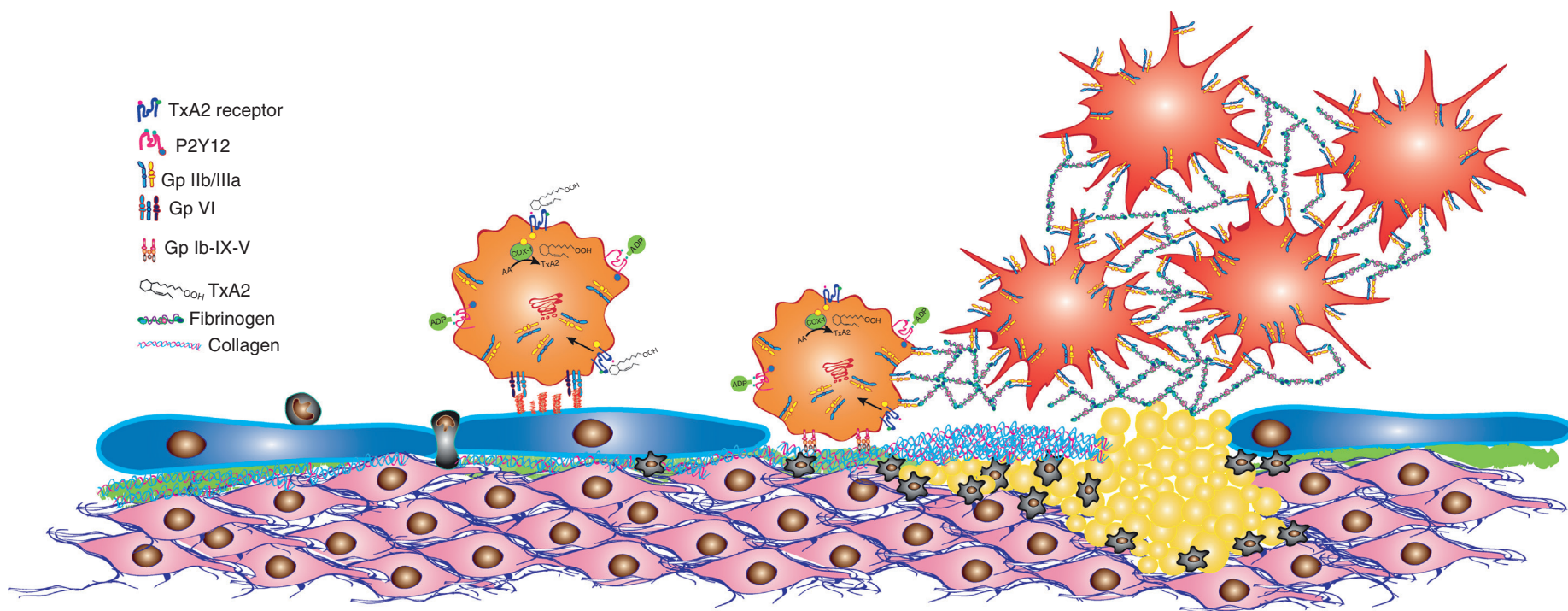


FIGURE 4.1 After vascular injury, platelet adhesion is generally the first step during which single platelets bind through specific membrane receptors (e.g., glycoprotein [GP] Ib/IX/V, GP VI) to the extracellular matrix constituents of the vessel wall (e.g., collagen, von Willebrand factor, fibronectin). Platelets then become activated and release multiple mediators, including thromboxane A₂ (TXA₂) and adenosine diphosphate (ADP), that bind to TXA₂ and P₂Y₁₂ receptors, respectively. Activation of the GP IIb/IIIa receptor, release of more vasoactive substances from the platelets, and platelet aggregation finally ensue.

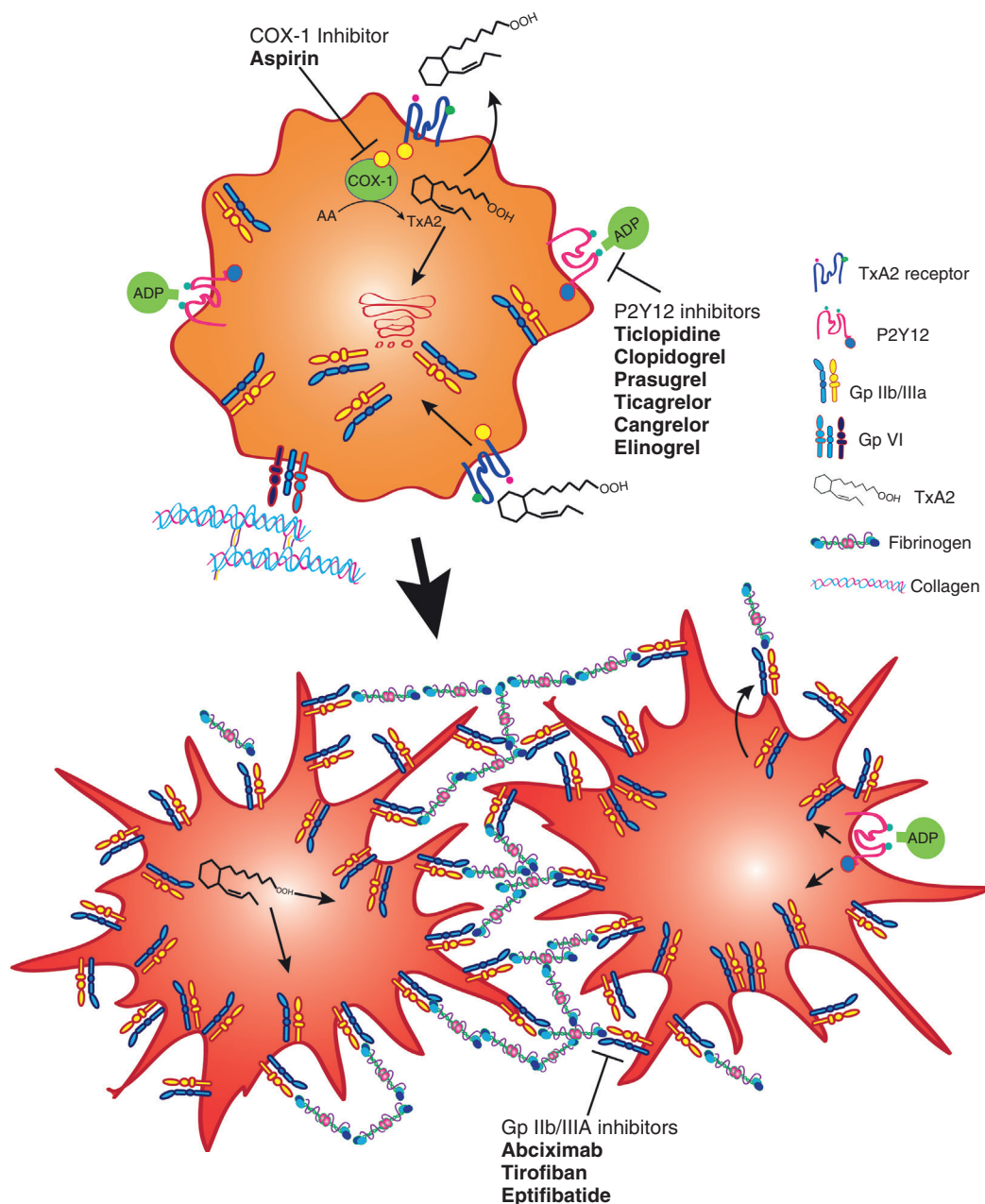


FIGURE 4.2 Thrombin and other agonists, such as adenosine diphosphate (ADP) and epinephrine, activate platelets and precipitate conformational changes in the glycoprotein (GP) IIb/IIIa receptor and platelet degranulation. This results in the release of more vasoactive substances such as serotonin, thromboxane A₂ (TXA₂), and more ADP, which bind to their receptors and cause activation of the GP IIb/IIIa receptor, further granule release, and ultimately promotes the common final pathway of platelet aggregation through the cross-linking of GP IIb/IIIa receptors on adjacent platelets by fibrinogen. AA, Arachidonic acid; COX, cyclooxygenase.

on the heart. More than a century later, aspirin is one the most commonly used medications worldwide. It is an inexpensive, safe, and effective antiplatelet drug that irreversibly inhibits cyclooxygenase, an enzyme responsible for the formation of eicosanoids (e.g., prostaglandin I₂ and TXA₂).⁶ Because TXA₂ promotes platelet aggregation, the acetylation of cyclooxygenase by aspirin decreases its generation in platelets and therefore platelet aggregability throughout the platelet's 7- to 10-day lifetime.⁷ Aspirin reaches appreciable plasma levels by 20 minutes and exerts its platelet-inhibitory effect within 60 minutes (Table 4.1). The use of enteric-coated and buffered formulations does not reduce the gastrointestinal (GI) bleeding

complications because these are largely related to aspirin's systemic effects.⁸

Aspirin Dosage

In a collaborative meta-analysis performed by the Antithrombotic Trialists' collaboration, low-dose aspirin (75–150 mg/day) was shown effective for long-term use.⁹ A substudy from the Percutaneous Coronary Intervention – Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) trial demonstrated that low-dose aspirin (≤ 100 mg) is effective in preventing ischemic events and causes lesser bleeding risk compared with higher doses.¹⁰ In the

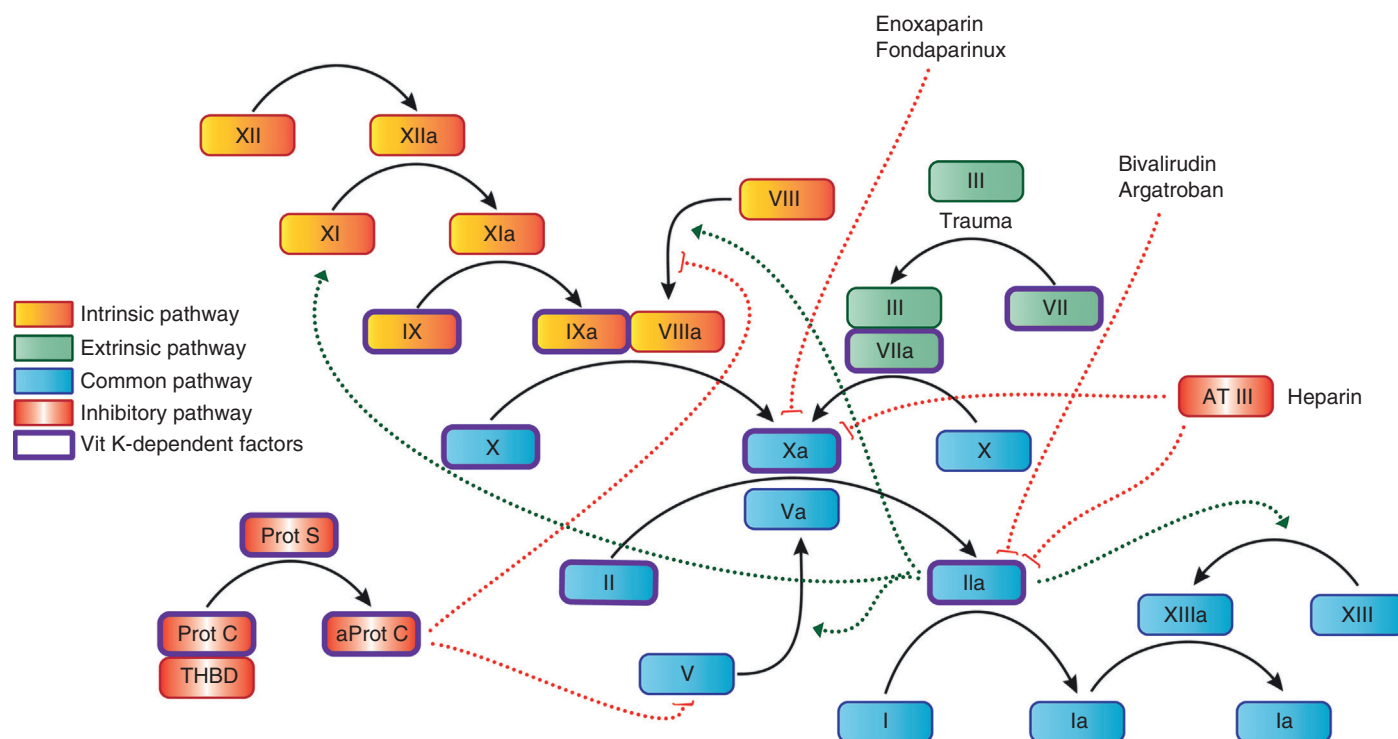


FIGURE 4.3 Coagulation proteins usually circulate in an inactive form in the blood. The coagulation cascade, triggered by vascular injury and exposure of tissue factor in the plaque to blood, consists of the intrinsic and extrinsic pathways. These two initially separate pathways ultimately converge on the common pathway and activate prothrombin to the active enzyme thrombin, which is important to catalyze the production of fibrin. Targets of the various anticoagulants used during percutaneous coronary intervention are shown. *aProt*, activated Protein; *AT*, Antithrombin; *Prot*, Protein; *THBD*, Thrombomodulin.

2016 American College of Cardiology/American Heart Association (ACC/AHA) Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease, Levine and colleagues¹¹ undertook a comprehensive assessment of aspirin dosing in patients undergoing PCI and endorsed a daily aspirin dose of 81 mg (range, 75–100 mg) as a Class I recommendation for PCI patients treated with dual antiplatelet therapy (DAPT).

Subsequently, the ADAPTABLE¹² (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness) trial findings were released in 2021 and confirmed the absence of significant differences in cardiovascular events and major bleeding between patients receiving 81 versus 325 mg/day of aspirin daily. ADAPTABLE was an open-label pragmatic trial randomizing patients ($n = 15,076$) with established atherosclerotic cardiovascular disease to either 81 or 325 mg/day of aspirin and found no differences in the primary effectiveness outcome (all-cause mortality, myocardial infarction [MI], or stroke) or safety (hospitalization for major bleeding) outcomes between both dosing regimens after a median follow-up period of 26 months.

Of note, the efficacy of ticagrelor appears reduced in patients treated with higher aspirin doses (≥ 300 mg/day); therefore, low-dose aspirin dose is what is preferred. The use of low-dose aspirin (81 mg in the United States, 75 mg or 100 mg elsewhere) is supported by the saturability of its antiplatelet effect at low doses, the lack of a dose-response relationship in studies evaluating its clinical anti-ischemic effects, and the dose-dependent response associated with its bleeding side effects.

ORAL P₂Y₁₂ RECEPTOR INHIBITORS

For more than a decade, DAPT with aspirin and clopidogrel has been the mainstay of antiplatelet management after PCI.¹³ Atherothrombotic events, however, continue to occur in a relevant proportion of patients despite the benefit of this combination, which has led to the clinical development of newer and more potent antiplatelet drugs. Two of these, prasugrel and ticagrelor, were approved for clinical use by the US Food and Drug Administration (FDA) in 2009 and 2011, respectively (see Table 4.1 and Video 4.1).

On the other hand, monotherapy with a P₂Y₁₂ inhibitor after a short DAPT period has emerged as a reasonable selective strategy to reduce the risk of bleeding in the contemporary PCI era. The TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial examined the safety of treating PCI patients with ticagrelor monotherapy after an initial 3-month course of DAPT (ticagrelor plus aspirin).¹⁴ TWILIGHT enrolled 7119 high-risk PCI patients (65% had non-ST segment elevation acute coronary syndrome [NSTEMI]; 63% multivessel coronary artery disease [CAD]) and demonstrated that ticagrelor monotherapy was associated with a lower incidence of bleeding than ticagrelor plus aspirin between randomization and 1 year, with no increase in ischemic events.

Ticlopidine

Ticlopidine was the first clinically used P₂Y₁₂ receptor inhibitor and demonstrated superiority (as part of a DAPT

TABLE 4.1 Oral Antiplatelet Drugs Used in Patients Undergoing Percutaneous Coronary Intervention

DRUG	ROUTE	REVERSIBILITY	DOSAGE	HALF-LIFE	TIME TO PLATELET INHIBITION	INDICATIONS	CONTRAINDICATIONS	TRANSITION TO CABG SURGERY	COMMENTS
Aspirin	Oral	Irreversible	81–325 mg/day	Dose dependent: 15–20 min for parent compound; 2–3 h after a single dose, and ≤2–19 h for higher doses	Varies according to formulation: within 30–60 min for immediate-release tablets; ≤45 min for coated tablets	All patients with CAD or clinical atherosclerotic CV disease	Hypersensitivity (i.e., anaphylaxis, urticaria, or bronchospasm) to aspirin, GI or active bleeding, severe thrombocytopenia	Recommended to be continued unless contraindications present—to be reinstituted within 6 h after CABG surgery	Available as a variety of formulations, including a rectal suppository; higher doses associated with GI toxicity; desensitization studies are considered in cases of allergy when long-term use is needed
Clopidogrel	Oral	Irreversible	Loading dose: 300–600 mg (a 600-mg loading dose is recommended at the time of PCI) Maintenance dose: 75 mg/day After a loading dose of 600 mg, a 150-mg/day dosage may be considered for the first 6 d and then 75 mg/day (as part of a double-dose clopidogrel regimen among patients with ACS undergoing PCI)	6 h	2 h	All patients with CAD or clinical atherosclerotic CV disease	Patients with active pathological bleeding (peptic ulcer, ICH); patients with hypersensitivity to clopidogrel; severe thrombocytopenia	5 d	Manufacturer warning of diminished effectiveness in poor metabolizers; labeling: avoid concomitant use with omeprazole or esomeprazole; CYP2C19 genotyping available but unproven; desensitization studied and considered for specific allergies when long-term use is needed
Prasugrel	Oral	Irreversible	Loading dose: 60 mg/day Maintenance dose: 10 mg/day (5 mg/day in patients with age 75 y or older or weight <60 kg)	2–15 h	1–2 h	Patients with ACS who are managed with PCI (after angiography to delineate the coronary anatomy)	Patients with active pathological bleeding (peptic ulcer, ICH); patients with hypersensitivity to prasugrel; severe thrombocytopenia Patients with previous TIA or stroke SHOULD NOT receive prasugrel (black box warning by FDA)	7 d	Much less variability in response; no benefit in medically managed patients or those 75 y or older unless they have prior MI or DM. A 5-mg dose is used in older adults (age 75 y or older) but remains unproven for CV outcomes
Ticagrelor	Oral	Reversible	Loading dose: 180 mg/day Maintenance dose: 90 mg twice daily	6–13 h	2 h (maximum platelet inhibition)	Patients with ACS, including patients who are managed with PCI or conservatively	Active bleeding, previous ICH, severe thrombocytopenia, severe bradycardia	5 d	Aspirin maintenance dose should not exceed 100 mg/day CYP3A4/5 substrate, so it is predisposed to numerous interactions: phenobarbital, carbamazepine, dexamethasone, rifampin, phenytoin may all decrease effectiveness Proven efficacy and safety in patients with ACS with CKD (compared with clopidogrel)

ACS, Acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; FDA, Food and Drug Administration; ICH, intracranial hemorrhage; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

regimen with aspirin) in reducing stent thrombosis and ischemic complications during coronary stenting.^{15,16} In a meta-analysis of studies comparing ticlopidine with clopidogrel in patients receiving coronary stents, clopidogrel had more tolerability and fewer side effects and was at least as effective as ticlopidine in reducing major adverse cardiovascular events (MACEs).¹⁷ Ticlopidine is a thienopyridine administered orally (250 mg twice daily). Its use was eclipsed by the use of safer and more potent P₂Y₁₂ receptor inhibitors, especially given its significant hematologic toxicity (e.g., neutropenia, agranulocytosis).

Clopidogrel

Mechanism of Action

Clopidogrel is a thienopyridine analog that binds irreversibly to the platelet ADP P₂Y₁₂ receptor and inhibits the binding of ADP to its receptor. It has a quicker onset of action and appears to be safer than ticlopidine. It is a pro-drug that requires a two-step hepatic bioconversion to its active metabolite.

Evidence

Clopidogrel has a similar clinical efficacy as ticlopidine in preventing stent thrombosis.^{18,19} Because of its better safety profile, it has replaced ticlopidine as the favored thienopyridine after stent implantation. The CREDO (Clopidogrel for the Reduction of Events During Observation) trial showed that long-term therapy (1 year) with clopidogrel after elective PCI significantly reduces the risk of MACEs.²⁰ A pretreatment strategy with clopidogrel at least 6 hours before PCI resulted in a lower incidence of the composite MACE in patients undergoing elective PCI compared with no reduction with treatment administered less than 6 hours before PCI.²⁰ The PCI-CURE trial demonstrated that among patients with NSTEMI-ACS undergoing PCI, pretreatment with clopidogrel followed by long-term therapy (for a mean of 8 months, on the background of aspirin therapy) was associated with a lower MACEs rate and no increase in major bleeding.¹³ The CLARITY (PCI-Clopidogrel as Adjunctive Reperfusion Therapy) trial extended the efficacy of clopidogrel to patients receiving fibrinolytics for ST-segment elevation myocardial infarction (STEMI).²¹

Indications

Clopidogrel is indicated for both patients with and without ACS undergoing PCI on top of aspirin.

Dosage

A loading dose of 600 mg of clopidogrel should be given to patients both with and those without ACS before PCI (Video 4.2). However, the loading dose of clopidogrel for patients undergoing PCI after fibrinolytic therapy should be 300 mg within 24 hours and 600 mg more than 24 hours after receiving fibrinolytic therapy. A 75-mg/day maintenance dose of clopidogrel is recommended thereafter.^{11,21}

Variability in Responsiveness to Clopidogrel

Limitations of clopidogrel include a broad variability in platelet inhibition, with a percentage of low responders

ranging from 5% to 40%, mostly attributable to genetic, cellular, and clinical mechanisms, including noncompliance.^{22,23} Poor responsiveness to clopidogrel is related to increased adverse ischemic outcomes.²³

The CURRENT-OASIS 7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes) trial investigators demonstrated that in patients undergoing PCI for ACS, a 7-day double-dose clopidogrel regimen was associated with a reduction in MACE and stent thrombosis compared with the standard dose.²⁴ This was proposed as a possible strategy to reduce the variability in response to clopidogrel.²⁵ However, the aforementioned findings were from a subgroup analysis from a trial that did not meet its prespecified primary outcome in the overall population studied.²⁶ Recent prospective randomized trials of platelet function testing (PFT) did not demonstrate clinical benefit. It is unclear whether treatment modification based on current PFT platforms can actually impact clinical outcomes.²⁷ Updated American and European practice guidelines have issued a Class IIb recommendation for PFT to facilitate the choice of P₂Y₁₂ receptor inhibitor in selective high-risk patients treated with PCI, although routine testing is not recommended (Class III). Importantly, recent data suggest that low on-treatment platelet reactivity to ADP may still be associated with a higher risk of bleeding, lending credence to the concept of a therapeutic window for P₂Y₁₂ inhibitor therapy.²³

Interaction with Proton Pump Inhibitors

The use of some proton pump inhibitors (PPIs) in conjunction with clopidogrel was shown to interfere with clopidogrel metabolism and to be associated with worse outcomes in pharmacodynamic and observational studies. The COSENT (Clopidogrel and the Optimization of Gastrointestinal Events) trial demonstrated no increase in cardiovascular ischemic events and a lower GI bleeding rate with the combination of clopidogrel and 20 mg omeprazole (in a single pill).²⁸ Thus, most patients can be safely treated with a PPI and clopidogrel, although there should be a clear indication for PPI therapy. According to the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease, the use of PPIs was deemed reasonable (Class IIa) in patients at high risk for GI bleeding (e.g., advanced age, prior known peptic ulcer disease, concomitant use of anticoagulants, or use of nonsteroidal antiinflammatory drugs).¹¹

The Role of Genotyping

Clopidogrel is a prodrug that requires conversion to its active metabolite through a two-step process in the liver that involves several *CYP450* isoenzymes, of which the *CYP2C19* isoenzyme is the most important.²⁹ At least three genetic polymorphisms of the *CYP2C19* isoenzyme are associated with loss of function. Multiple prospective studies of P₂Y₁₂ inhibitors demonstrated higher rates of cardiovascular events in patients who have loss-of-function *CYP2C19* gene variants among patients receiving clopidogrel.³⁰ Genotyping for a *CYP2C19* loss-of-function variant in patients treated with clopidogrel may be considered



selectively if results of testing are expected to alter management.^{25,29} Decisions regarding genotyping should be made on an individual basis because no definitive outcome data support utility and cost-effectiveness in the general population.

Prasugrel

Mechanism of Action

Prasugrel is a thienopyridine prodrug that requires conversion to an active metabolite before binding to the platelet P_2Y_{12} receptor to confer antiplatelet effects.³¹ Prasugrel inhibits ADP-induced platelet aggregation faster, more consistently, and to a greater extent than clopidogrel.

Evidence

The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) compared prasugrel head to head with clopidogrel among patients with ACS (STEMI and NSTEMI) undergoing PCI.³² During a 15-month median follow-up period, prasugrel was superior to clopidogrel in reducing the relative risk of the composite endpoint of cardiovascular death, MI, or stroke by 19% (2.2% absolute risk reduction), which was driven predominantly by a significant reduction in nonfatal MI.³² Stent thrombosis and urgent target vessel revascularization were also reduced by prasugrel. However, prasugrel was associated with higher rate of the key safety endpoint (major bleeding) and more life-threatening and fatal bleeding events.³²

Indications

Prasugrel is indicated for the treatment of patients with ACS (STEMI and NSTEMI) undergoing PCI on top of aspirin. The use of prasugrel in patients without ACS undergoing PCI is not well studied and is off-label use. Its risk-to-benefit ratio in medically treated patients with ACS is similar to clopidogrel, but given that it is more expensive than clopidogrel, prasugrel in general should not be used in the medical management of ACS.³³

Dosage

A 60-mg loading dose of prasugrel should be administered as soon as possible for patients with STEMI and after the coronary anatomy is delineated and before PCI among patients with NSTEMI.³² A 10-mg/day maintenance dose of prasugrel should be continued thereafter.

Additional Considerations

Post hoc analyses demonstrated that underweight patients (<60 kg) and older adults (75 years of age or older) had no net clinical benefit, but patients with prior stroke or transient ischemic attack (TIA) experienced net clinical harm with prasugrel.³² Prasugrel should not be given to patients with ACS who have a prior history of stroke or TIA ("black box warning" by the FDA).¹¹ Despite greater and more consistent inhibition of ADP-dependent platelet function and MACE reduction, there is still interpatient variability in on-treatment platelet reactivity with prasugrel, albeit less than with clopidogrel.³⁴⁻³⁶

Ticagrelor

Mechanism of Action

Unlike the thienopyridines clopidogrel and prasugrel, ticagrelor is a reversible and direct-acting oral antagonist of the ADP receptor P_2Y_{12} .³⁷ It provides faster, greater, and more consistent P_2Y_{12} inhibition than clopidogrel.³⁷

Evidence

The PLATO (Study of Platelet Inhibition and Patient Outcomes) trial was a randomized controlled trial (RCT) comparing ticagrelor versus clopidogrel for the prevention of vascular events among 18,624 patients with ACS (STEMI and NSTEMI).³⁸ Compared with clopidogrel, ticagrelor reduced the composite endpoint of vascular death, MI, or stroke by 16% (absolute risk reduction, 1.9%), which was driven by reduction in both MI and vascular death events. Notably, ticagrelor treatment resulted in absolute risk reduction in an overall mortality rate of 1.4% compared with clopidogrel at 12-month follow-up.³⁸ Although ticagrelor was not associated with an increased rate of trial-defined major bleeding, it had a higher rate of major non-coronary artery bypass grafting (CABG)-related bleeding and more fatal intracranial bleeding.³⁸

Indications

Ticagrelor is indicated in patients with ACS (STEMI and NSTEMI) undergoing PCI, as well as in those with medically treated ACS, on top of low-dose aspirin (75, 81, or 100 mg).^{38,39}

Dosage

An oral loading dose of 180 mg of ticagrelor should be administered as early as possible or at the time of PCI followed by a maintenance dose of 90 mg twice daily.

Additional Considerations

Because of its reversible inhibition of the P_2Y_{12} receptor, ticagrelor is associated with quicker functional recovery of circulating platelets and a faster offset of effect than clopidogrel. This may theoretically pose a problem for noncompliant patients, especially given its twice-daily dosing regimen.²⁵ The FDA issued a boxed warning indicating that aspirin daily maintenance doses greater than 100 mg decrease the effectiveness of ticagrelor and cautioned against its use in patients with active bleeding or a history of intracranial hemorrhage. Among clopidogrel nonresponders, the direct-acting ticagrelor therapy inhibited platelet reactivity below the cut points associated with ischemic risk.³⁵ Ticagrelor also demonstrated superior efficacy and comparable safety to clopidogrel among patients with chronic kidney disease (CKD) (estimated glomerular filtration rate <60 mL/min).⁴⁰ Thus, ticagrelor is a useful P_2Y_{12} receptor inhibitor in patients with CKD.⁴¹

Duration of Therapy with Oral P_2Y_{12} Receptor Inhibitors

Irrespective of the stent type, patients undergoing PCI for ACS should receive an oral P_2Y_{12} receptor inhibitor for at least 12 months,^{12,32,38} on the background of aspirin therapy. Among patients without ACS undergoing PCI with

a drug-eluting stent (DES), an oral P₂Y₁₂ receptor inhibitor should be administered for at least 6 months.¹¹ On the other hand, patients without ACS undergoing PCI with a bare-metal stent (BMS) should receive an oral P₂Y₁₂ receptor inhibitor for a minimum of 1 month and ideally up to 6 months (although a shorter 2-week course may be acceptable if the patient is at very high bleeding risk).^{11,20} In DES-treated PCI patients who have a high risk of bleeding or develop significant overt bleeding, it may be reasonable to discontinue P₂Y₁₂ inhibitor therapy after 6 months in those with ACS and after 3 months in those without ACS.¹¹ Overall, the optimal duration of DAPT after PCI with stenting depends on the initial patient presentation (ACS or stable ischemic heart disease [SIHD]) as well as patient-specific ischemic and bleeding risks. In patients with high ischemic and low bleeding risks, continuation of DAPT (beyond 6 and 12 months for those with SIHD and ACS, respectively) should be undertaken after engaging in a shared decision-making process. The DAPT risk score is one of many objective prediction tools that can help guide decisions about duration of DAPT.⁴² The score was developed from a large dataset of patients receiving DES and BMS in the DAPT trial and helps predict net clinical benefit (i.e., combined ischemic and bleeding risks) and identifies patients who benefit from extended DAPT duration (12–30 months). If ticagrelor is chosen as part of a prolonged DAPT strategy beyond 12 months, using a 60 mg twice-daily dosing regimen is reasonable.⁴³

Recently, the OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice) trial compared 3-month versus 12-month DAPT durations in low-risk patients (stable CAD or low-risk ACS) who underwent PCI using zotarolimus-eluting stents.⁴⁴ A 3-month DAPT duration was proven noninferior to a 12-month regimen with respect to the composite endpoint (all-cause death, MI, stroke, or major bleeding) and did not increase the risk of stent thrombosis.⁴⁴

According to the 2014 ACC/AHA perioperative guideline,⁴⁵ elective noncardiac surgery after PCI with DES may be considered after 180 days if the risk of further delay is greater than the expected risks of ischemia and stent thrombosis.

Choice of Oral P₂Y₁₂ Receptor Inhibitor Therapy

Prasugrel and ticagrelor each showed superiority to clopidogrel in an RCT,^{32,38} with ticagrelor in particular demonstrating a respectable mortality benefit. The 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease recommended (Class I recommendation) the use of DAPT in all patients undergoing PCI with stenting, whether presenting with ACS or SIHD, but supported the preferential use of ticagrelor or prasugrel over clopidogrel in patients with ACS (Class IIa recommendations) in the absence of contraindications, an approach that was similarly adopted by the European guidelines.^{11,25} Similarly, the 2014 AHA/ACC NSTEMI-ACS guideline stated that it is reasonable to choose ticagrelor or prasugrel over clopidogrel for P₂Y₁₂ inhibition in appropriate clinical settings (in patients with ACS and for prasugrel in PCI-treated patients with ACS

only).⁴⁶ Clopidogrel (75 mg/day) is the preferred P₂Y₁₂ receptor inhibitor in most stable patients.¹¹

The ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) 5 trial was a randomized trial comparing ticagrelor with prasugrel in 4018 patients with ACS in whom an invasive evaluation was planned. Prasugrel was associated with a lower incidence of the composite ischemic endpoint (death, MI, or stroke) but no differences in major bleeding rates.^{47,48} The findings of this investigator-initiated open-label trial need to be confirmed in future trials.

Use of Oral P₂Y₁₂ Receptor Inhibitors with Fibrinolytic Therapy

Timely fibrinolytic therapy should be administered to achieve prompt reperfusion among acute STEMI patients presenting to a non-PCI-capable hospital and who cannot be transferred to a PCI-capable hospital for primary PCI within 120 minutes.⁴⁹ In these patients, the use of a 75-mg/day dose of clopidogrel (on top of aspirin) has been shown to reduce short-term mortality rates and major cardiovascular events without increasing major bleeding hazards.⁵⁰ There is a paucity of data demonstrating the clinical utility and safety of the newer oral P₂Y₁₂ receptor inhibitors in patients receiving fibrinolytic therapy.

Timing of Discontinuation of Oral P₂Y₁₂ Receptor Inhibitor Therapy

Among patients undergoing planned CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days and prasugrel for at least 7 days before elective surgery to reduce the need for blood transfusion.^{11,25,49,51} Among patients undergoing urgent CABG, these agents should be discontinued for at least 24 hours to reduce major bleeding complications.⁵¹

Antithrombotic Therapy in Patients Receiving Long-Term Anticoagulation

For patients who undergo PCI with stenting and requiring chronic oral anticoagulant (OAC) therapy (e.g., atrial fibrillation), a dual antithrombotic strategy (OAC + P₂Y₁₂ receptor inhibitor) has become a mainstay treatment. The Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation (AUGUSTUS) trial was a randomized trial that examined the safety and efficacy of apixaban versus a vitamin K antagonist and of low-dose aspirin versus placebo (all on the background of P₂Y₁₂ inhibitor therapy for 6 months) among 4614 patients with atrial fibrillation and recent ACS or PCI.⁵² AUGUSTUS demonstrated that a regimen including apixaban without aspirin resulted in lesser bleeding but no differences in ischemic events compared with regimens that included a vitamin K antagonist, aspirin, or both.

In the immediate post-PCI period, it is reasonable to discharge patients on an OAC (preferably a direct oral anticoagulant [DOAC]) plus a P₂Y₁₂ receptor inhibitor and aspirin. Aspirin can then be dropped after 1 or 4 weeks, depending on whether the patient is at low or high thrombotic risk, respectively, and then continue with a dual

antithrombotic strategy for a 12-month period. In patients without ACS, clopidogrel is a reasonable P_2Y_{12} receptor inhibitor to be used with a DOAC. In patients with ACS, the choice can be either clopidogrel or ticagrelor, with ticagrelor preferred in patients at high risk for ischemic complications. After the completion of a 12-month dual antithrombotic strategy, the P_2Y_{12} receptor inhibitor can be dropped and the patient continued on long-term DOAC monotherapy (unless the patient is at high risk for thrombotic complications, at which time continuation with dual strategy is reasonable).⁵³

Oral Glycoprotein IIb/IIIa Receptor Inhibitors

Four oral GP IIb/IIIa inhibitors were examined in randomized clinical trials and demonstrated increased mortality risk and significantly higher bleeding rates.⁵⁴ The development and use of oral GP IIb/IIIa inhibitors were therefore halted.

INTRAVENOUS ANTIPLATELET DRUGS

Intravenous Glycoprotein IIb/IIIa Receptor Inhibitors

There are two clinically used intravenous (IV) GP IIb/IIIa inhibitors, tirofiban and eptifibatide (Table 4.2). (A third agent, abciximab, was discontinued by the manufacturer and is no longer available in the United States.) Although these agents have a role in selective clinical settings, their use has diminished with the advent and widespread use of P_2Y_{12} receptor inhibitors and newer anticoagulants.

Mechanism of Action

The GP IIb/IIIa receptor is the most abundant receptor on the platelet surface and is responsible for the last common pathway of platelet aggregation, and GP IIb/IIIa receptor inhibitors interfere with platelet cross-linking and thrombus formation by competing with fibrinogen and von Willibrand factor for GP IIb/IIIa binding.

Evidence

Evidence supporting the use of IV GP IIb/IIIa receptor inhibitors predates the era of widespread DAPT and the advent of bivalirudin. Earlier studies showed the efficacy of IV GP IIb/IIIa receptor inhibitors in reducing periprocedural ischemic complications—mostly periprocedural MI—during PCI among patients treated with aspirin and heparin.⁵⁵⁻⁵⁹

In the contemporary era, the strongest evidence supporting the use of GP IIb/IIIa inhibitors came from the ISAR-REACT-2 RCT of 2022 patients with NSTEMI-ACS undergoing PCI who were adequately pretreated with DAPT (with all patients receiving 600 mg of clopidogrel at least 2 hours before the procedure).⁶⁰ In this study, abciximab conferred a significant 3% absolute risk reduction and a 25% relative risk reduction at 30 days in the composite ischemic endpoint of death, MI, or urgent target vessel revascularization.⁶⁰ The benefits of abciximab were confined to patients presenting with elevated troponin. In the era of adequately treated patients with DAPT, the benefits of GP IIb/IIIa inhibitors are inconsistent and less conclusive among

patients with STEMI,^{61,62} and the benefits appear to be among patients with the highest risk profile.⁶³ Similarly, contemporary trials of patients pretreated with aspirin and clopidogrel have not demonstrated any benefit with GP IIb/IIIa inhibitor therapy in patients with stable symptoms undergoing elective PCI.⁶⁴

Therefore, these agents should not be used routinely but rather selectively, such as in patients with large thrombus burden and in those who are not adequately preloaded with a P_2Y_{12} receptor inhibitor and as a bailout strategy for thrombotic complications during the PCI procedure.

Indications

In patients undergoing primary PCI who are receiving unfractionated heparin (UFH), administration of an IV GP IIb/IIIa inhibitor was a routine practice in patients not pretreated with an oral P_2Y_{12} receptor inhibitor because it helps mitigate periprocedural thrombotic complications and MI. In the contemporary PCI era in which adequate pretreatment with DAPT is routine, the merits of IV GP IIb/IIIa inhibitors are less certain. These agents may, however, be selectively useful in patients with ACS with high-risk features (e.g., elevated troponin, STEMI) who are treated with UFH but not adequately pretreated with a P_2Y_{12} receptor inhibitor or who have a heightened risk for ischemic complications.

Intravenous GP IIb/IIIa inhibitors are also advocated in patients with refractory ischemia and those undergoing high-risk PCI or as bailout therapy for thrombotic complications occurring during PCI (e.g., distal embolization, jailed side branch, wire on thrombus, side-branch closure, obstructive dissection, IC thrombus, persistent residual stenosis, prolonged ischemia). IV GP IIb/IIIa inhibitors should not be routinely used during PCI for vein graft diseases because they have not shown to be beneficial in this setting.⁶⁵ The use of GP IIb/IIIa inhibitors is likely to further decline with the use of the newer and more potent P_2Y_{12} receptor inhibitors.

Dosage

Double-bolus eptifibatide (180-mcg/kg bolus followed 10 minutes later by a second 180-mcg/kg bolus) and high-bolus dose tirofiban (25 mcg/kg) have been adopted to achieve a high degree of platelet inhibition^{66,67} (see Table 4.2).

Duration of Therapy

Eptifibatide and tirofiban are usually given intraprocedurally and administered for up to 18 to 24 hours. Longer infusions are associated with increased bleeding hazards and thrombocytopenia and should be avoided unless absolutely necessary. Shorter durations of infusions (<18 hours) may be safe even in patients with high-risk NSTEMI-ACS⁶⁸ and in certain clinical scenarios can be even abbreviated to less than 2 hours, which is a more commonly adopted approach in the contemporary era of potent oral DAPT.⁶⁹

Additional Considerations

Routine use of GP IIb/IIIa receptor inhibitors is not recommended in patients receiving bivalirudin as the primary anticoagulant but may be considered as a bailout strategy in selective cases.¹¹

TABLE 4.2 Intravenous Antiplatelet Drugs in Patients Undergoing Percutaneous Coronary Intervention

DRUG	ROUTE	DOSE	DOSE ADJUSTMENT	ROUTE OF ELIMINATION	HALF-LIFE	INDICATIONS	CONTRAINDICATIONS
Eptifibatide	IV	Double-bolus is advocated: IV 180- μ g/kg bolus followed 10 min later by a second IV 180- μ g/kg bolus Maintenance dose: 2 μ g/kg/min ($\leq$ 15 mg/h) for $\leq$ 72 h	Cr Cl <50 mL/min/1.73 m ² : 180- μ g/kg/min IV bolus followed by 1 μ g/kg/min for $\leq$ 72 h Contraindicated in patients on hemodialysis	Primarily renal	2.5 h	In patients undergoing elective PCI with stenting and receiving UFH, it is reasonable to use a GP IIb/IIIa inhibitor when patients are not adequately pretreated with clopidogrel Even among patients with stable CAD adequately pretreated with clopidogrel, it may be reasonable to administer a GP IIb/IIIa inhibitor Among patients with NSTEMI-ACS with high-risk features who are not adequately pretreated with clopidogrel and who are receiving UFH, it is useful at the time of PCI to administer a GP IIb/IIIa inhibitor Even among patients with NSTEMI-ACS adequately pretreated with clopidogrel, it is reasonable at the time of PCI to administer a GP IIb/IIIa inhibitor In patients undergoing primary PCI for STEMI treated with UFH, it is reasonable to administer a GP IIb/IIIa inhibitor, whether or not patients were pretreated with clopidogrel	Hypersensitivity; active bleeding; recent GI or GU bleed; recent surgery; recent CVA; bleeding diathesis; thrombocytopenia; severe hypertension Should not be used routinely as an upstream strategy for patients with ACS undergoing PCI
Tirofiban	IV	High-bolus dose is advocated: 25 μ g/kg over 3 min followed by a maintenance dose of 0.15 μ g/kg/min for $\leq$ 18 h	Cr Cl <30 mL/min/1.73 m ² : reduce maintenance dose by 50%	Primarily renal	2 h	In patients undergoing elective PCI with stenting and receiving UFH, it is reasonable to use a GP IIb/IIIa inhibitor when patients are not adequately pretreated with clopidogrel Even among patients with stable CAD adequately pretreated with clopidogrel, it may be reasonable to administer a GP IIb/IIIa inhibitor Among patients with NSTEMI-ACS with high-risk features who are not adequately pretreated with clopidogrel and who are receiving UFH, it is useful at the time of PCI to administer a GP IIb/IIIa inhibitor Even among patients with NSTEMI-ACS adequately pretreated with clopidogrel, it is reasonable at the time of PCI to administer a GP IIb/IIIa inhibitor In patients undergoing primary PCI for STEMI treated with UFH, it is reasonable to administer a GP IIb/IIIa inhibitor, whether or not patients were pretreated with clopidogrel	Hypersensitivity; active bleeding; recent GI or GU bleed; recent surgery; recent CVA; bleeding diathesis; thrombocytopenia; severe hypertension Should not be used routinely as an upstream strategy for patients with ACS undergoing PCI
Cangrelor	IV	30-mcg/kg bolus before PCI followed immediately by an infusion of 4 mcg/kg/min continued for at least 2 h or for the duration of the PCI, whichever is longer	No dosage adjustment necessary for patients with kidney or hepatic impairment	Rapidly inactivated in the circulation by dephosphorylation to its primary metabolite, a nucleoside with negligible antiplatelet activity; platelet function normalizes within 60 min after discontinuation	$t_{1/2}$ elimination = 3–6 min	Indicated for use as an adjunct to PCI to reduce the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a P ₂ Y ₁₂ receptor inhibitor or received a GP IIb/IIIa inhibitor Its use as a bridge therapy before cardiac surgery remains off-label use	Significant active bleeding or known hypersensitivity

ACS, Acute coronary syndrome; CAD, coronary artery disease; Cr Cl, creatinine clearance; CVA, cardiovascular accident; GI, gastrointestinal; GP, glycoproteins; GU, genitourinary; IV, intravenous; MI, myocardial infarction; NSTEMI-ACS, non-ST segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; $t_{1/2}$, half-life; UFH, unfractionated heparin.



Timing of Administration of Glycoprotein IIb/IIIa Receptor Inhibitor

Upstream precatheterization use of GP IIb/IIIa inhibitors among STEMI patients undergoing PCI is not recommended given the lack of efficacy,^{62,70} and the increased risk of bleeding (irrespective of the reperfusion strategy). Among patients with NSTEMI-ACS pretreated with DAPT, routine upstream administration of eptifibatide (≥ 12 hours before angiography) was not superior to its provisional use during PCI and was actually associated with increased risk of bleeding and transfusions.⁷¹

Choice of Intravenous Glycoprotein IIb/IIIa Receptor Inhibitor

In a meta-analysis of five RCTs comparing abciximab with the small-molecule GP IIb/IIIa inhibitors among patients undergoing primary PCI, no outcome differences (short-term mortality, reinfarction, bleeding) were seen between the STEMI groups.⁷² Another meta-analysis among patients with STEMI undergoing primary PCI confirmed similar results between abciximab and the small molecules in terms of angiographic, electrocardiographic, and clinical outcomes.⁷³ Thus, all GP IIb/IIIa inhibitors seem to perform equally, even in the highest thrombotic risk subset of patients, and the benefits of GP IIb/IIIa receptor inhibitors do not appear to be drug specific but rather a class effect. Abciximab was recently discontinued in the United States by the manufacturer, and only the small-molecule IV GP IIb/IIIa inhibitors are currently available.

Timing of Discontinuation of Glycoprotein IIb/IIIa Receptor Inhibitors

Eptifibatide and tirofiban should be discontinued 2 to 4 hours or more before urgent CABG. Platelet transfusions are indicated in patients receiving GP IIb/IIIa receptor inhibitors who have active life-threatening bleeding, especially among patients treated with abciximab (though repeat transfusions may be necessary). They are, however, not directly effective in reversing the effects of the small molecules eptifibatide or tirofiban, though they are still useful to reverse any aspirin or clopidogrel effect. Fresh-frozen plasma or cryoprecipitate alone or in combination with platelet transfusions can help reverse the antiplatelet effects in patients treated with eptifibatide and tirofiban. In addition, tirofiban is dialyzable, and immediate hemodialysis can be done when needed.

Cangrelor

Cangrelor, a nonthienopyridine adenosine triphosphate analog, is a direct-acting, selective, and specific inhibitor of the P_2Y_{12} receptor with a very short half-life (3–6 minutes). Platelet function normalizes within 30 to 60 minutes after its discontinuation. Thus, cangrelor is likely to play a role in patients who require rapid, predictable, and profound but reversible platelet inhibition. The CHAMPION PCI (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition PCI)⁷⁴ and CHAMPION

PLATFORM (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition PLATFORM)⁷⁵ RCTs examined cangrelor administered during PCI and showed no benefit of cangrelor compared with clopidogrel or placebo with respect to ischemic outcomes. On the other hand, the CHAMPION PHOENIX (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition PHOENIX) trial included 11,145 patients who were undergoing urgent or elective PCI and were receiving guideline-recommended therapies to receive a bolus or infusion of cangrelor or a 300- to 600-mg loading dose of clopidogrel.⁷⁶ Cangrelor significantly reduced the rate of ischemic events, including stent thrombosis, during PCI without increasing severe bleeding events.⁷⁶ Pooled patient-level data from all three aforementioned trials comparing cangrelor with control (clopidogrel or placebo) for prevention of PCI-related thrombotic complications demonstrated that cangrelor reduced PCI thrombotic complications, albeit at the expense of increased bleeding.⁷⁷ Cangrelor was approved by the FDA in 2015 as an adjunct to PCI to reduce the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a P_2Y_{12} receptor inhibitor or received a GP IIb/IIIa inhibitor. Its use at a lower dose as a bridge therapy before cardiac surgery or other procedures remains off label.

INTRAVENOUS ANTICOAGULANT DRUGS

An anticoagulant (Table 4.3) should be administered to all patients undergoing PCI, in addition to at least two antiplatelet drugs, to prevent IC thrombus formation at the site of arterial injury or on the interventional equipment (e.g., guidewire, catheter). Before the procedure, all patients should be evaluated for bleeding risk, which also predicts post-PCI death. Strategies to reduce bleeding risk should be implemented, such as the use of lower bleeding risk agents (e.g., bivalirudin), weight-adjusted dosing of heparin, activated clotting time (ACT) and activated partial thromboplastin time (aPTT) monitoring, dose adjustment in CKD patients, and use of radial artery access.⁷⁸

Unfractionated Heparin

Unfractionated heparin is the oldest and most commonly used anticoagulant during PCI. It is easy to administer, fast acting, and easily monitored and can be reversed with protamine. The ability to reverse it makes it the preferred anticoagulant for use during PCI of chronic total occlusion (CTO) lesions.

Mechanism of Action

Unfractionated heparin is an indirect antithrombin drug made of a mixture of glycosaminoglycans of varying lengths with a high affinity for the antithrombin enzyme.

Evidence

Although it is widely used, there are no prospective RCTs demonstrating its efficacy (vs placebo) during PCI.

TABLE 4.3 Commonly Used Parenteral Anticoagulant Drugs During Percutaneous Coronary Intervention

PARENTERAL ANTICOAGULANT MEDICATIONS	ROUTE	DOSE	DOSE ADJUSTMENT	ROUTE OF ELIMINATION	HALF-LIFE	CONTRAINDICATIONS
UFH	IV	70–100 U/kg without GP IIb/IIIa or 50–70 U/kg with GP IIb/IIIa to rebolus (e.g., 1000–5000 U) according to ACT levels	Without GP IIb/IIIa: adjust to achieve a target ACT of 250–300 s (HemoTec assay) or 300–350 s (Hemochron assay) with GP IIb/IIIa: adjust to achieve an ACT of 200–250 s	Liver and reticuloendothelial system	1.5 h (range, 1–6 h) [follows zero-order kinetics]	Active bleeding, HIT, HITT
Enoxaparin	SC	1 mg/kg SC every 12 h for medically treated ACS IV 0.3 mg/kg enoxaparin should be administered at the time of PCI to patients who received <2 therapeutic SC doses or received the last SC dose 8–12 h before PCI If undergoing PCI >12 h after the last SC enoxaparin dose, patients should receive full-dose de novo anticoagulation regimen If undergoing PCI ≤8 h of the last SC dose (and already received multiple SC doses), no more enoxaparin is needed If no prior anticoagulation is given, an IV bolus of 0.5–0.75 mg enoxaparin should be administered during PCI	Decrease to 1 mg/kg SC daily in patients whose Cr Cl <30 mL/min	Liver and renal clearance if 10% of active dose	4.5 h (range, 3–6 h)	Active bleeding, HIT, HITT
Fondaparinux	SC	2.5 mg SC daily	Avoid if Cr Cl <30 mL/min/1.73 m ²	Primarily renal	17–21 h	Severe renal impairment, hypersensitivity, active bleeding, weight <50 kg, thrombocytopenia
Bivalirudin	IV	0.75-mg/kg IV bolus followed by 1.75 mg/kg/h during PCI (and ≤ 4 h post procedure, if needed) If continued anticoagulation is needed after the initial 4 h after PCI, the infusion may be continued for up to an additional 20-h period at 0.2 mg/kg/h	Cr Cl = 10–30 mL/min/1.73 m ² : reduce infusion to 1 mg/kg/h	Renal (20%), proteolytic cleavage (80%)	25 min (normal renal function)	Hypersensitivity, active bleeding

ACS, Acute coronary syndrome; ACT, activated clotting time; Cr Cl, creatinine clearance; HIT, heparin-induced thrombocytopenia; HITT, heparin-induced thrombotic thrombocytopenia; IV, intravenous; GP, glycoprotein; PCI, percutaneous coronary intervention; SC, subcutaneous; UFH, unfractionated heparin.

Indications

In the absence of other anticoagulants and despite the paucity of high-level evidence, IV UFH is indicated during PCI. Routine postprocedural heparin is not recommended in patients with uncomplicated PCI procedures. Anticoagulation with UFH monotherapy, on the background of aspirin alone, is insufficient during PCI to protect against thrombotic complications, and in this instance, at least a second antiplatelet agent (an oral P₂Y₁₂ agent or an IV GP IIb/IIIa inhibitor) should be added.

Dosage

Dosing differs depending on whether an IV GP IIb/IIIa inhibitor is used or not. In the absence of GP IIb/IIIa inhibitor therapy, a 70- to 100-U/kg bolus of UFH (up to a maximum of 10,000 units) should be administered during PCI (and before wiring the coronary artery) to achieve a target ACT of 250 to 300 seconds (when using the HemoTec assay) or 300 to 350 seconds (when using the Hemochron assay). In the presence of an IV GP IIb/IIIa inhibitor, a 50- to 70-U/kg bolus of UFH should be used to achieve an ACT of 200 to 250 seconds. Additional boluses should be administered as needed (usually in 2000- to 5000-U increments) to maintain the aforementioned ACT goals during PCI, with ACT checks undertaken usually at 10-minute intervals. Although still widely used, both the Hemochron and HemoTec assays for measuring ACT are imprecise.⁷⁹ Moreover, the relationship between ACT levels and outcomes and thus the utility of measuring ACT during PCI remain uncertain.⁸⁰ Similar dosing regimen and ACT goals apply to PCIs performed using the radial approach.

Additional Considerations

Unfractionated heparin has many limitations, including platelet activation, inability to bind clot-bound thrombin, a narrow therapeutic window, and an unpredictable anticoagulant effect. It can also cause heparin-induced thrombocytopenia (HIT) or even the rare heparin-induced thrombotic thrombocytopenia (HITT) syndrome.⁸¹ After PCI, a femoral sheath is usually removed when the ACT is less than 150 to 180 seconds (or when the aPTT becomes <50 seconds). UFH should not be administered to patients who already received recent subcutaneous enoxaparin because of difficulty in dosing and increased bleeding rate.⁸²

Enoxaparin

Mechanism of Action

Enoxaparin is a low-molecular-weight heparin (LMWH; 3–5 kDa) with greater activity against factor Xa than thrombin. It has more predictable and consistent anticoagulation effects⁸³ and carries a lower risk of HIT and HITT than UFH.

Evidence

Comparative studies showed inconsistent benefits of enoxaparin over UFH during PCI.^{82,84–87} A large meta-analysis of randomized trials ($n = 13$ studies; 7318 patients) comparing LMWH (mostly enoxaparin) versus UFH as anticoagulants during PCI demonstrated a significant reduction in the risk of major bleeding with LMWHs (odds ratio, 0.57; 95% confidence interval, 0.40–0.82) but without differences in ischemic outcomes.⁸⁸

Indications

Intravenous enoxaparin may be reasonable during PCI for patients who have not received prior anticoagulant therapy or who have received upstream subcutaneous enoxaparin for NSTEMI-ACS (Class IIb).¹¹

Dosage

Enoxaparin can be administered subcutaneously (usually as upfront therapy in patients with ACS) or IV (usually during PCI). Patients with ACS who are initially treated medically usually receive 1 mg/kg of subcutaneous enoxaparin twice daily. An additional dose of 0.3 mg/kg IV enoxaparin should be administered at the time of PCI to patients who have received less than two therapeutic subcutaneous doses or received the last subcutaneous dose 8 to 12 hours before PCI.⁸⁹ Patients undergoing PCI more than 12 hours after the last subcutaneous enoxaparin dose should receive a full-dose de novo anticoagulation regimen, and those who undergo PCI 8 hours or less after the last subcutaneous dose (and already received multiple subcutaneous doses) are usually adequately anticoagulated and do not require additional treatment (Video 4.3). For those who have not received prior anticoagulant therapy, an IV bolus of 0.5 to 0.75 mg/kg of enoxaparin was established to be safe and efficacious compared with UFH in the STEEPLE (Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation) trial.⁹⁰ Anti-Xa levels are not routinely measured during PCI.

Additional Considerations

Despite a better safety profile and more evidence, enoxaparin is infrequently used in modern interventional suites. Enoxaparin is generally less popular because of many shortcomings, including but not limited to its longer half-life, its inability to reverse completely with protamine, the complexity of dosing, and the need for dose adjustment among patients with CKD.

Bivalirudin

Mechanism of Action

Bivalirudin is a synthetic polypeptide that acts as a direct thrombin inhibitor. Unlike heparins, bivalirudin binds to thrombin in both its clot-bound and fluid phases and inactivates thrombin directly. Additional advantages of bivalirudin include its short-half-life (25 minutes), lack of need for anticoagulation monitoring, and lack of platelet activation. In addition, it does not cause HIT or HITT and is the agent of choice (along with argatroban) in these patients.

Evidence

Bivalirudin has been studied in multiple PCI settings: elective PCI,^{91–93} NSTEMI-ACS,^{93,94} and STEMI.⁹⁵ Earlier studies demonstrated that bivalirudin is associated with reduced bleeding and is, for the most part, noninferior in terms of ischemic outcomes to the combination of UFH and IV GP IIb/IIIa inhibitor. Notably, bivalirudin reduced the cardiac mortality rate in patients with STEMI undergoing primary PCI (an effect that can be only partially attributable to differences in bleeding).⁹⁶ This mortality benefit is controversial

and was not observed in other trials, such as the EURO-MAX (European Ambulance Acute Coronary Syndrome Angiography) trial.⁹⁷ EUROMAX, which used upstream bivalirudin and had increased radial access and novel P₂Y₁₂ inhibitor use, reconfirmed, however, the risk of early stent thrombosis with bivalirudin in primary PCI.⁹⁷ Adequate clopidogrel pretreatment (with a 600-mg dose) is likely to mitigate any potential hazards of early thrombosis that may arise with bivalirudin.⁹⁸ The HEAT-PPCI (How Effective Are Antithrombotic Therapies in Primary PCI) trial compared anticoagulation with bivalirudin versus UFH during primary PCI for STEMI, on the background of similar GP IIb/IIIa inhibitor use (14%).⁹⁹ In this single-center study, UFH reduced the incidence of MACE compared with bivalirudin and did not increase bleeding risk.⁹⁹ These provocative findings were attributed by some to methodologic shortcomings (e.g., open-label design, single center, adjudication of events).¹⁰⁰ Overall, the previously observed clinical benefits of bivalirudin over UFH (e.g., lower bleeding hazards) may be less apparent in the contemporary era of radial artery access and reduced use of GP IIb/IIIa inhibitors, though in STEMI, the benefit does still persist even in the most recent datasets.

Indications

Bivalirudin is useful as an anticoagulant with or without prior UFH treatment across the full spectrum of patients with CAD undergoing PCI. Bivalirudin is the anticoagulant of choice among patients with HIT.

Dosage

Bivalirudin is administered as a 0.75-mg/kg IV bolus followed by 1.75-mg/kg/h IV infusion for the duration of the PCI procedure (and ≤4 hours after the procedure if needed) (see [Table 4.3](#)).

Additional Considerations

The lower bleeding rate imparted by bivalirudin is eliminated when used concomitantly with an IV GP IIb/IIIa inhibitor. Notably, the bailout rates with GP IIb/IIIa inhibitors in the major bivalirudin trials were consistently around 7%.^{91,94,95} Some shortcomings of bivalirudin are (1) it has no antidote and cannot be reversed ([Video 4.4](#)), thus, it should generally be avoided during CTO PCI; (2) when used alone (and without adequate DAPT pretreatment), patients with ACS may sustain slightly excess thrombotic risk (especially acute stent thrombosis risk); and (3) it is more expensive than UFH.

Fondaparinux

Mechanism of Action

Fondaparinux is a synthetic pentasaccharide that indirectly inhibits factor Xa but has no effect on thrombin.

Evidence

The OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) trial assessed fondaparinux use in patients with ACS undergoing PCI and demonstrated similar rates of ischemic event at 9 days but substantially

improved bleeding and long-term mortality rates compared with enoxaparin.¹⁰¹

Indications

Fondaparinux is indicated for patients with NSTEMI-ACS and should be continued for the duration of hospitalization or until PCI is performed.⁴⁶ Concerns about catheter-associated thrombosis were evident in clinical trials,^{101,102} and fondaparinux should therefore never be used alone during PCI. An anticoagulant with anti-IIa activity (either UFH or bivalirudin) should be administered with fondaparinux to mitigate this risk.¹¹

Dosage

Patients with ACS are usually treated with a once-daily subcutaneous injection of 2.5 mg of fondaparinux for the duration of hospitalization or until PCI.

Additional Considerations

Fondaparinux is limited by its long half-life (17–20 hours) and is contraindicated in patients with severe CKD (because of its predominant renal excretion). Monitoring of anti-Xa activity is not needed, and fondaparinux does not affect aPTT or ACT levels.

Other Parenteral Anticoagulants

Argatroban is another IV direct thrombin inhibitor that was approved in 2002 by the FDA for patients undergoing PCI who have HIT or are at risk of developing it.¹⁰³ Unlike bivalirudin, it can be used in patients with CKD. However, it is excreted by the liver and should be avoided in patients with significant hepatic dysfunction.

Duration of Anticoagulation Therapy After Percutaneous Coronary Intervention

Prolonged anticoagulation after PCI results in excessive bleeding and prolonged length of stay with no reduction in ischemic outcomes. Unlike oral DAPTs, anticoagulants should not be routinely continued after PCI¹⁵ unless a compelling reason exists for the use of triple agents (e.g., atrial fibrillation, prosthetic valve).

VASODILATORS AND ANTIHYPERTENSIVE DRUGS

Hypertension Urgency or Emergency

A large proportion of patients referred for cardiac catheterization have baseline hypertension, predominantly essential hypertension. Often these patients experience hypertension exacerbation in the cardiac catheterization laboratory. Anxiety, missing antihypertensive medication doses before the procedure, and volume overload during PCI can all be predisposing factors. Poorly controlled hypertension during coronary angiography or PCI may predispose patients to myocardial ischemia and create myocardial oxygen demand–supply mismatch. It is therefore important to become familiar with the treatment of acute



hypertension crises in cardiac catheterization with the goal to alleviate myocardial ischemia but without compromising coronary perfusion or depressing the heart contractile function. Vasodilators such as nitroglycerin are especially attractive because they mitigate the effects of hypertension, reduce wall stress, alleviate ischemia, and promote coronary vasodilation. Hypertensive emergencies are usually characterized by ongoing end-organ damage and warrant the use of parenteral agents of rapid onset and offset action. However, sudden rapid declines in blood pressure may be hazardous and should be avoided.

The No-Reflow Phenomenon

The no-reflow phenomenon occurs usually as a result of distal embolization, vasospasm, or endothelial injury, and often complicates PCI of degenerated vein grafts, ectatic coronary arteries, and heavily thrombotic lesions. It is more common after STEMI and is reported to occur in approximately 30% of patients undergoing primary PCI.¹⁰⁴ In one study of 489 patients with STEMI treated at four primary PCI centers, no-reflow phenomenon was the only independent predictor of MACE at 1-year follow-up.¹⁰⁵ No-reflow phenomenon may be associated with more cases of congestive heart failure, cardiogenic shock, and death. Therefore, prompt treatment is essential. Intracoronary vasodilators (e.g., adenosine, nitroprusside) are reasonable for the treatment of patients with PCI-associated no-reflow phenomenon. In the case of no-reflow phenomenon, it is best to administer the vasodilator drug in the distal

portion of the vessel via a microcatheter (or through the lumen of a distally advanced over-the-wire balloon catheter) rather than at the tip of the guide catheter to ensure delivery to the microvascular bed.

Selective Vasodilators and Antihypertensive Medications (Table 4.4)

Nitroglycerin

Nitroglycerin is a vasoactive nitric oxide (NO) donor that reduces ischemia through its predominant venodilatory effect, which reduces preload, left ventricular wall stress, and myocardial oxygen demand. NO helps inhibit platelet adhesion and has also antiinflammatory activity. It is commonly administered via the IV or sublingual routes in a cardiac catheterization laboratory. Given its short duration of action, an IV infusion of nitroglycerin (5–10 mcg/min; ≤ 200 mcg/min) is relatively selective for the venous capacitance vessels and is especially useful in patients with PCI-complicated ischemia and/or heart failure. At higher doses (>200 mcg/min), IV nitroglycerin can vasodilate large conductance vessels and is effective in treating hypertension urgency. Nitroglycerin also dilates the epicardial coronary arteries and large arterioles (>100 μ m), so they can improve coronary perfusion and mitigate vasospasm (e.g., catheter-induced spasms) when used IC (usually 100- to 400-mcg IC boluses) (Video 4.5B). Nitroglycerin has no effect on the microcirculation, does not induce hyperemia, and has limited use in the treatment of no-reflow phenomenon.

TABLE 4.4 Overview of Commonly Used Parenteral Anti-Hypertensive Drugs in Cardiac Catheterization

ANTI-HYPERTENSIVE MEDICATIONS	DOSE		DRUG KINETICS AND METABOLISM		SYSTEMIC EFFECTS			
	INITIAL	MAXIMUM			CO	HR	SVR	ADVERSE EFFECTS
Nitroglycerin	Initial: 5 mcg/min increased by 5 mcg/min every 3–5 min ≤ 20 mcg/min; then increased by 10–20 mcg/min every 3–5 min	200 mcg/min	$t_{1/2}$: 1–4 min	Hepatic, plasma	$\leftrightarrow/\downarrow$	$\leftrightarrow/\uparrow$	$\downarrow$	Hypotension, headache, rash, tachyphylaxis, methemoglobinemia
Nitroprusside	Initial: 0.25–0.3 mcg/kg/min increased by 0.5 mcg/kg/min to 3 mcg/kg/min	10 mcg/kg/min	$t_{1/2}$: 2 min	Plasma	$\uparrow$	$\leftrightarrow/\uparrow$	$\downarrow\downarrow$	Cyanide poisoning, cardiac dysrhythmia, hypotension, hemorrhage, bowel obstruction, metabolic acidosis, methemoglobinemia
Esmolol	50 mcg/kg/min (titrate by 50 mcg/kg/min every 5 min)	300 mcg/kg/min	$t_{1/2}$: 9 min Onset: immediate	Esterases, renal	$\downarrow$	$\downarrow\downarrow$	$\downarrow$	Bradycardia, dizziness, drowsiness, hypotension, heart block
Labetalol	IV: bolus 10–20 mg over 2 min; then 0.5–2 mg/min (titrate by 0.5 mg/min every hour)	8 mg/min not to exceed 300 mg/day	$t_{1/2}$: 2.5–8 h (normal renal function)	Hepatic (glucuronidation), biliary, renal (minimal $\sim 5\%$)	$\downarrow$	$\downarrow\downarrow$	$\downarrow$	Bradycardia, dizziness, drowsiness, hypotension, heart block, orthostatic hypotension, syncope
Nicardipine	Initial: 5 mg/hr increased by 2.5 mg/hr every 5–15 min Maintenance: 3 mg/hr	15 mg/hr	$t_{1/2}$: 2–4 h	Hepatic, plasma	$\downarrow$	$\leftrightarrow/\uparrow$	$\downarrow$	Acute hepatitis, myocardial ischemia, headache, hypotension

CO, Cardiac output; HR, heart rate; IV, intravenous; SVR, systemic vascular resistance; $t_{1/2}$, half-life.

Adenosine

Intracoronary adenosine (40- to 100-mcg boluses) is often used during PCI to vasodilate the microcirculation to prevent or treat the no-reflow phenomenon.^{106,107} In a meta-analysis of 10 RCTs comparing adenosine versus placebo among patients with ACS, adenosine was associated with a 75% reduction in post-PCI no-reflow phenomenon.¹⁰⁸ However, no benefits on mortality rate or clinical outcomes were observed with the adjunctive use of adenosine therapy.¹⁰⁸

Both IC boluses and IV infusion of adenosine are used to induce maximal hyperemia during invasive physiological assessment of intermediate coronary lesions, such as fractional flow reserve (FFR). Although IC adenosine (≥ 40 - to 100-mcg boluses) is easier to use, more cost effective, and has fewer systemic side effects, IV adenosine (usually at 140 mcg/kg/min, sometimes at 180 mcg/kg/min) achieves more consistent and prolonged hyperemia and is particularly useful to evaluate ostial lesions and when slow pull-back across a diffusely diseased vessel is needed.¹⁰⁹ A small study ($n = 45$) recently demonstrated that high incremental doses of IC adenosine (≤ 600 mcg) allows obtaining FFR values similar to IV adenosine and is not associated with increased side effects.¹¹⁰

Adenosine is also valuable in diagnosing and treating supraventricular tachycardias that occur during PCI. Adenosine can induce atrioventricular (AV) block and bradycardia, necessitating the use of a temporary transvenous pacemaker in some instances, and should be cautiously used in patients with conduction abnormalities and in patients with advanced bronchospastic airway disease. Fortunately, it has a short half-life, and its effect is usually quickly dissipated (5–10 seconds) through metabolism by the red blood cells.

Nitroprusside

Sodium nitroprusside is a direct NO donor and potent vasodilator that rapidly reduces ventricular filling pressure and systemic vascular resistance. It has a very rapid onset of action (2–5 minutes), and its effect quickly dissipates after discontinuing the infusion. IV nitroprusside is therefore ideal for treatment of heart failure and among patients with post-MI mechanical complications. Prolonged infusions, particularly in the setting of renal or hepatic disease, may result in the uncommon but serious side effect of cyanide or thiocyanate toxicity. IC nitroprusside (100- to 200-mcg boluses) is also effective in treating slow-flow or no-reflow phenomenon^{111–113} and may be beneficial in its prevention.¹¹⁴

Ca²⁺ Channel Antagonists

Ca²⁺ channel antagonists reduce blood pressure and improve coronary flow through peripheral and coronary arterial vasodilation, suppress myocardial contractility, and reduce heart rate (through suppression of sinoatrial node automaticity and AV conduction). They are therefore very good anti-ischemic and antihypertensive agents but can also precipitate heart failure in predisposed patients (especially the cardioselective agents). Verapamil, diltiazem, and the dihydropyridines have fundamental differences with respect to pharmacologic characteristics and effects. The cardioselective verapamil and diltiazem have potent antihypertensive effects but also exert

negative chronotropic and inotropic effects on the heart, whereas the dihydropyridines exert predominantly vascular effects (with minimal effects on cardiac contractility) and are very effective antihypertensive drugs. The dihydropyridines, such as nicardipine, are more potent vasodilators than verapamil, which is more potent than diltiazem. IV nicardipine (5–15 mg/h) can be used during hypertensive urgencies, although it can exacerbate myocardial ischemia and cause hypotension.

Intracoronary nicardipine is a safe and highly effective pharmacologic agent to reverse no-reflow phenomenon during PCI (mean dose in one study, 460 mcg).¹¹⁵ Early administration of IC verapamil during direct PCI also improves postprocedural myocardial perfusion, as evaluated by Thrombolysis in Myocardial Infarction (TIMI) myocardial perfusion grade.¹¹⁶ IC diltiazem (50–200 mcg) or verapamil (50–200 mcg) can reverse the no-reflow phenomenon more effectively than nitroglycerin during primary PCI for acute MI.¹¹⁷ The efficacies of diltiazem and verapamil are similar, although diltiazem seems safer.¹¹⁷ In one study of 347 identified patients with STEMI treated with PCI, nicardipine, nitroprusside, and verapamil were equally effective in improving flow.¹⁰⁴ Overall, pharmacologic treatment normalized coronary flow in 40% of patients assessed by myocardial blush grade and in 79% of patients assessed using the TIMI score.¹⁰⁴

Beta-Adrenergic Receptor Antagonists

Beta-Adrenergic receptor antagonists are effective in treating patients with hypertensive crises and reducing myocardial O₂ consumption through negative chronotropic and inotropic effects and by decreasing arterial blood pressure. In patients with limited cardiac reserve who are critically dependent on adrenergic stimulation, beta-receptor blockers may cause profound reduction in left ventricular function and cause or exacerbate heart failure and cardiogenic shock. For the latter reasons, beta-blockers are not advocated any more as an upfront clinical performance measure to be implemented within 24 hours of presentation after acute myocardial infarction (AMI),¹¹⁸ and their parenteral use should be particularly avoided given the increased hazards of cardiogenic shock.¹¹⁹

Intravenous labetalol (10- to 20-mg bolus followed by a 0.5- to 2-mg/min infusion up to 300-mg total cumulative dose) may be useful during adrenergic crises in the catheterization laboratory, as in patients presenting with cocaine-associated ACS and hypertensive crisis.¹²⁰ Given its short half-life, IV esmolol (50–300 mcg/kg/min) may be particularly useful in patients with acute aortic syndromes presenting for preoperative angiography (often in conjunction with IV nitroprusside) to rapidly reduce blood pressure and the shear stress on the aortic wall (though most of these patients should go directly to surgery without angiography).

VASOPRESSORS AND INOTROPIC DRUGS

Hypotension

There are myriad reasons for hypotension occurring during coronary interventions. Appropriate treatment depends on prompt and accurate diagnosis of the precipitating cause.

A sudden decrease in blood pressure within minutes of radiocontrast material is usually attributable to an anaphylactic reaction with vasodepressor response (confirmed by low left-ventricular end diastolic pressure on left heart catheterization). Treatment in this case should be immediate volume resuscitation and epinephrine. After complicated femoral arterial access, vascular hemorrhage is usually suspected. Wire exit and coronary perforation are in the differential diagnosis, and pericardiocentesis and discontinuation or reversal of anticoagulants should be instituted in such cases. Arrhythmias and valvular lesions (e.g., critical aortic stenosis, acute ischemic mitral regurgitation) have differing therapies (e.g., antiarrhythmic medications, cardioversion, balloon valvuloplasty, revascularization). Cardiogenic shock is usually diagnosed by right heart catheterization and arterial hemodynamic monitoring (combination of elevated intracardiac pressures, depressed cardiac index, and low systemic arterial pressure) and should be treated with a combination of vasopressors or inotropes, percutaneous ventricular assist devices (pVADs), and revascularization in most instances. A decrease in blood pressure as a result of transient myocardial ischemia during PCI can be managed by an IV bolus of phenylephrine (50–100 mcg), which has pure alpha-adrenergic agonist activity and therefore augments arterial blood pressure by increasing systemic vascular resistance with minimal effects on contractility or heart rate. In all the aforementioned scenarios, vasopressors are the initial treatment strategy (with or without volume repletion) irrespective of the inciting cause and on top of the definitive treatment (e.g., revascularization, blood transfusions, vascular repair).

Acute Heart Failure or Cardiogenic Shock

Acute heart failure may develop in the cardiac catheterization laboratory as a result of multiple interrelated causes, including volume overload from increased contrast use, pulmonary vascular redistribution during prolonged cases, iatrogenic from inappropriate and overzealous beta-blockers or Ca^{2+} channel blocker use, arrhythmias, myocardial ischemia during PCI (in cases of acute closure, distal embolization, or myocardial stunning), and myriad other causes. Initial therapy requires airway protection with intubation and mechanical ventilation, in addition to inotropic support, aggressive diuresis, and possibly pVADs. Also, around 6% to 8% of patients with AMI develop cardiogenic shock, of whom up to 60% to 75% may develop during hospitalization. Many of these occurred in a cardiac catheterization laboratory and require adding vasopressors to inotropic support.¹²¹

Selective Vasopressors and Inotropes (Table 4.5)

Phenylephrine

It is a synthetic alpha-agonist catecholamine that causes predominantly peripheral vasoconstriction. It is used to treat patients with acute hypotension resulting from myocardial ischemia, stunning or no-reflow phenomenon during PCI, or complicating dynamic left ventricular outflow obstruction. It is usually given IV in 50- to 100-mcg incremental boluses.

Dopamine

Dopamine is an endogenous parenteral catecholamine-like agent that is useful in the treatment of hypotension, heart failure, and cardiogenic shock. Its pharmacodynamic effects differ with escalating doses, with low doses (2 mcg/kg/min) usually causing splanchnic vasodilation and enhanced natriuresis, moderate doses (2–8 mcg/kg/min) inducing beta₁-adrenergic receptor activation in the heart, and high doses (>8 mcg/kg/min) stimulating peripheral vasoconstriction and predominant vasopressor effects by acting as an alpha₁ sympathomimetic. A maximal inotropic effect is likely seen at a 5-mcg/kg/min dose. Dopamine is useful to treat patients with hypotension and shock in the cardiac catheterization laboratory by imparting a vasopressor effect and increasing cardiac output. However, it can cause tachycardia and exacerbate arrhythmias and myocardial ischemia, which may limit its use.

Norepinephrine

Norepinephrine is an endogenous catecholamine with selective beta₁ (but not beta₂) sympathomimetic activity and strong alpha₁ and alpha₂ sympathomimetic effects. IV norepinephrine (2–4 mcg/min up to 30 mcg/min) is a potent vasoconstrictor with fewer inotropic and chronotropic effects than epinephrine and dopamine and causes less arrhythmia than either agent. In a multicenter RCT of 1679 patients with shock, dopamine was compared head to head against norepinephrine as first-line vasopressor therapy to restore and maintain blood pressure.¹²² Although no significant intergroup differences in 28-day mortality rate were observed, there were more arrhythmias among dopamine-treated patients.¹²² In the subgroup of 280 patients with cardiogenic shock, norepinephrine was associated with a lower mortality rate.¹²² Norepinephrine may produce mesenteric vasoconstriction and cause splanchnic ischemia and resultant septicemia.

Dobutamine

Dobutamine is a parenteral sympathomimetic that activates both beta₁ and beta₂ but has few effects on alpha-adrenergic receptors. It is the preferred inotrope after an AMI when a pure inotropic response is desired but not a vasopressor effect that may exacerbate ischemia. Dobutamine does not increase the infarct size or cause significant arrhythmias and is also preferred to dopamine in patients with heart failure because of its vasodilatory actions (through β -2 receptor activation). An IV infusion of 2 to 20 mcg/kg/min is typically used. Hypotension may ensue sometimes with its use, and thus low-dose dopamine may be co-administered with it. Infrequently, a low- to moderate-dose dobutamine infusion may be used in the cardiac catheterization laboratory to induce pharmacologic stress and examine contractile reserve and valvular stenosis severity (e.g., in low-output aortic stenosis).

Epinephrine

Epinephrine is a sympathomimetic drug that activates alpha-, beta₁-, and beta₂-adrenergic receptors. At low doses, it increases the cardiac output through its beta₁-adrenergic effects (because the alpha-receptor-induced vasoconstriction

TABLE 4.5 Overview of Parenteral Vasopressors and Inotropes Commonly Used in Cardiac Catheterization Laboratories

	DOSE	DRUG KINETICS AND METABOLISM	CO	SYSTEMIC EFFECTS		ADVERSE EFFECTS	ROUTE OF ADMINISTRATION	
				HR	SVR			
Vasopressors								
Dopamine	Initial: 5–10 mcg/kg/min Maximum: 50 mcg/kg/min (adults)	t _{1/2} : 2–5 min	Renal, hepatic, plasma	5–10 mcg/kg/min: ↑ >10 mcg/kg/min: ↑	5–10 mcg/kg/min: ↑ >10 mcg/kg/min: ↑↑	5–10 mcg/kg/min: ↔/↑ >10 mcg/kg/min: ↑↑	Angina, ectopic beats, dyspnea, nausea or vomiting, headache, tachycardia	Continuous IV infusion
Norepinephrine	Initial: 8–12 mcg/min, titrate to desired response Maintenance: 2–4 mcg/min Maximum: 30 mcg/min Post cardiac arrest: 0.1–0.5 mcg/kg/min	t _{1/2} : 1 min	Renal, hepatic, plasma	↔/↓	↑	↑↑	Arrhythmia, reflex bradycardia, headache, extravasation, dyspnea	Continuous intravenous infusion
Phenylephrine	Initial: 20–180 mcg/min or 0.5 mcg/kg/min; titrate to desired response Maintenance: 40–60 mcg/min (given also as 100-mcg IV boluses for transient hypotension episodes in the catheterization lab)	t _{1/2} : 5 min	Hepatic	↔	↔/↓	↑	Arrhythmia, extravasation, pulmonary edema, MI	Continuous IV infusion
Epinephrine	Hypotension or shock: Initial: 0.1–0.5 mcg/kg/min to be titrated to the desired response Anaphylaxis: IM or SC: 0.2–0.5 mg (1:1000) every 5–15 min IV: 0.1 mg (1:1000) over 5 min or may infuse at 1–4 mcg/min Asystole or pulseless VT or VF: Usually: 1 mg IV every 3–5 min until restoration of spontaneous circulation	t _{1/2} : 2 min	Uptake and metabolism in the adrenergic neurons (by monoamine oxidase and so on) Hepatic metabolism for circulating drug	↑	↑	↔/↓ at low doses ↑ at high doses	Arrhythmias, splanchnic vasoconstriction and mesenteric ischemia, hypertension, pallor, anxiety, pulmonary edema	Continuous IV infusion IV, IM, and SC routes are used during anaphylaxis IV, IO, and endotracheal routes are acceptable for asystole and pulseless VF or VT
Vasopressin	Cardiac arrest: 40 units given once as an alternative to the first or second dose of epinephrine Maintenance: 0.02–0.04 units/min	t _{1/2} : 10–20 min; ~18 min	Hepatic, renal	↔	↔	↑	Arrhythmia, extravasation, dyspnea, water intoxication syndrome, anaphylaxis	IV, IO, or endotracheal; continuous IV infusion
Inotropes								
Dobutamine	Initial: Acute cardiac decompensation: –1–20 mcg/kg/min Maximum: 40 mcg/kg/min	t _{1/2} : 2 min	Hepatic	↑	↑	↔/↓	Arrhythmia, angina, nausea, dyspnea, tachycardia	Continuous IV infusion
Milrinone	Initial loading dose (optional): 50 mcg/kg over 10 min Maintenance: 0.125–0.750 mcg/kg/min	t _{1/2} : 2.5 h	Hepatic (12%)	↑	↑	↓	Arrhythmias, hypotension, chest pain or angina, headache	Continuous IV infusion

CO, Cardiac output; HR, heart rate; IM, intramuscular; IO, intra-osseous; IV, intravenous; MI, myocardial infarction; SC, subcutaneous; SVR, systemic vascular resistance; $t_{1/2}$, half-life; VF, ventricular fibrillation; VT, ventricular tachycardia.



is offset by the β_2 receptor–induced vasodilation). At higher doses, the α -adrenergic receptor vasoconstrictor effect predominates, causing an increase in cardiac output and systemic vascular resistance. In the cardiac catheterization laboratory, it is used for the treatment of asystole and pulseless ventricular tachycardia and ventricular arrhythmias (usually 1 mg IV every 3–5 minutes until return of spontaneous circulation) and for the treatment of anaphylaxis (0.2- to 0.5-mg intramuscular or subcutaneous injections to be repeated every 5–15 minutes as needed; 0.1-mg IV bolus over 5 minutes; or 1- to 4-mcg/min IV infusion for refractory patients). It can be used for treatment of patients with bradycardia and severe hypotension as well.

Additional Agents

Vasopressin is an antidiuretic hormone analog that has important vasopressor actions, especially in patients with extreme shock. It can be administered IV at 0.01 to 0.04 U/min. During cardiac arrest, a 40-U bolus may be administered IV (or endotracheal). IV milrinone (0.125–0.750 mcg/kg/min) is an inotropic agent that inhibits phosphodiesterase III and increases cardiac contractility and is independent of the action of the β -adrenergic receptors. It is useful in patients with heart failure but can induce peripheral arterial and venous dilation and consequent hypotension, as well as exacerbate arrhythmias.

PROCEDURAL SEDATION: ANXIOLYTICS AND ANALGESICS

Most PCIs are performed under minimal sedation (anxiolysis) or moderate sedation (depressed consciousness with the ability to respond to verbal commands) (Table 4.6).¹²³ Deep sedation is infrequently used in catheterization laboratories and usually requires the presence of an anesthesiologist for airway protection.

Benzodiazepines (e.g., midazolam, lorazepam, diazepam) are sedating agents used to provide anxiolysis and anterograde amnesia. Midazolam is very commonly used because of its short half-life and is usually given as 0.5- to 1-mg IV boluses to be repeated every 5 minutes for up to a maximum of 0.1 to 0.2 mg/kg. Benzodiazepines should, however, be complemented by an opioid (e.g., fentanyl, morphine sulfate), which can provide an analgesic effect (Table 4.7). Fentanyl (25- to 100-mcg IV boluses) is fast acting, has a rapid offset of action after small bolus doses, does not release histamine, and imparts minimal cardiovascular depression. Fentanyl is therefore the preferred analgesic in patients undergoing PCI, especially those with poor cardiac function. IV propofol is a very fast-acting sedative (<1 minute) with a short duration of action that can be used for monitored anesthesia care sedation (0.5-mg/kg slow injection over 3–5 minutes followed by a 25- to 75-mcg/kg/min infusion); however, it can cause profound hypotension and cardiorespiratory depression. Thus, its use in nonintubated patients by nonanesthesiologists is not routinely recommended.

MISCELLANEOUS DRUGS

Antiarrhythmic Medications

Arrhythmias may occur in patients undergoing invasive cardiac procedures. They can be caused by myocardial ischemia, increased sympathoadrenal tone from pain or anxiety, or catheter manipulation of cardiac structures (e.g., during right heart catheterization) or can occur as a result of poor left ventricular contractile function. IV lidocaine is a Class IB drug that is particularly useful in the treatment of ventricular arrhythmias occurring in the setting of myocardial ischemia. Lidocaine-associated proarrhythmias are uncommon; however, central nervous system side effects may occur, with nystagmus being an early sign of lidocaine toxicity (Table 4.8). IV amiodarone is effective in acutely terminating ventricular tachycardia¹²⁴ and is supplanting lidocaine as first-line therapy in these patients (see Table 4.8).¹²⁵ It is often used in the treatment of patients with atrial fibrillation with rapid ventricular response. Prompt electrical cardioversion and defibrillation remain the cornerstone therapies for unstable arrhythmias and ventricular fibrillation. Adenosine is an antiarrhythmic agent that slows AV nodal conduction and interrupts reentry pathways through the AV node. It has a very rapid onset and a brief duration of action (<10-second half-life) and is typically used for the treatment of patients with paroxysmal supraventricular tachycardia (6- to 12-mg IV boluses) in the cardiac catheterization laboratory. Atropine is an anticholinergic agent with a rapid onset of action and short half-life (2–3 hours) that is often used in the cardiac catheterization laboratory to treat bradycardia (0.5 mg IV every 3–5 minutes, not to exceed 3 mg).

Diuretics

Loop diuretics are the most powerful diuretic agents and act to reduce sodium chloride reabsorption in the kidneys. They are the agents of choice in patients who develop acute pulmonary edema and volume overload in the cardiac catheterization laboratory. In the presence of normal renal function, a 40-mg furosemide IV bolus (equivalent to 1 mg of bumetanide or 20 mg of torsemide) can achieve a maximal diuretic effect with a 15-minute onset of action. However, in the presence of congestive heart failure or renal insufficiency, a two- to fivefold increase in dose may be needed. Loop diuretics may cause hypovolemia, hypotension, and electrolyte abnormalities.

CONCLUSIONS

There is a large armamentarium of pharmacotherapies that invasive cardiologists can choose from. Because new evidence, indications, and medications are forthcoming, it is important that invasive cardiologists remain continuously updated and constantly familiar with the evolving trends. It is also preferable that operators and all staff in cardiac catheterization laboratories focus on the use of a

TABLE 4.6 Overview of Commonly Used Parenteral Sedatives in Cardiac Catheterization

DOSE					PREFERRED ROUTE OF ADMINISTRATION	REVERSAL AGENT	ADVERSE EFFECTS	
ANXIOLYTICS	INITIAL	MAXIMUM	DRUG KINETICS AND METABOLISM					
Benzodiazepines								
Midazolam	0.02–0.04 mg/kg IV; usual dose is 1–2 mg IV bolus (consider lower initial doses in older adults or when given concomitantly with analgesics); 0.07–0.08 mg/kg or 5 mg IM 30–60 min prior	Until desired clinical response or 0.1–0.2 mg/kg; usually no more than 5 mg IV needed for induction unless prior history of heavy alcohol use	Onset: 2–5 min Duration: <2 h (single dose)	$t_{1/2}$: 2–6 h (prolonged in renal failure, older adults, cirrhosis, and HF)	Hepatic	IV injection (may give IM)	Flumazenil (0.2 mg every min ≤1 mg)	Amnesia, respiratory depression, hypotension, headache, drowsiness or oversedation, nausea or vomiting, pain, and injection site reactions
Lorazepam	0.044 mg/kg IV; usual dose is 2 mg; 0.05 mg/kg or 2 mg IM 2 h prior	4 mg IV or IM	Onset: 2–3 min Duration: ≤8 h	$t_{1/2}$: ≈12–14 h	Hepatic	IV injection (may give IM)		Amnesia, respiratory depression, hypotension, drowsiness or oversedation, dizziness, headache, propylene glycol toxicity (lactic acidosis, hyperosmolality, hypotension) with IV use in renal failure, pain, and injection site reactions
Nonbenzodiazepine								
Propofol	50–150 mcg/kg/min (3–9 mg/kg/h)	Until desired clinical response or 200 mcg/kg/min (12 mg/kg/h)	Onset: 30 s Duration: 3–10 min	$t_{1/2}$ (biphasic): initially ≈40 min; terminal 4–7 h but ≤1–3 d if prolonged infusion (≈10 d)	Hepatic	IV injection or infusion	None	Respiratory depression, hypotension, pruritus, involuntary movement, pain or injection site reactions, apnea, hypertriglyceridemia, zinc deficiency
Etomidate	0.2–0.4 mg/kg IV for induction, 5–15 mcg/kg/min for maintenance	0.6 mg/kg IV for induction; 20 mcg/kg/min for maintenance	Onset: 30–60 s Duration: 3–5 min	$t_{1/2}$: ≈1.25–2.6 h	Hepatic	IV injection or infusion		Respiratory depression, pain and injection site reaction, involuntary movements, nausea or vomiting, apnea, adrenal suppression, propylene glycol toxicity (renal failure)

HF, Heart failure; IM, intramuscular; IV, intravenous; $t_{1/2}$, half-life.

TABLE 4.7 Overview of Commonly Used Parenteral Analgesics in Cardiac Catheterization

DOSE			DRUG KINETICS AND METABOLISM			PREFERRED ROUTE OF ADMINISTRATION	REVERSAL AGENT	ADVERSE EFFECTS
ANALGESICS	INITIAL	MAXIMUM						
Fentanyl	25–100 mcg IV or IM up to every 3 min	Doses >200 mcg rarely needed unless chronic opioid user	Onset (IV): immediate to within minutes; (IM): ≈7–8 min Duration (IV): dose dependent ≈0.5–1 h after single dose but increases with repeated doses (IM): 1–2 h (respiratory effects may persist longer than analgesia)	$t_{1/2}$: 2–4 h (increases with repeated doses)	Hepatic or intestinal	IV injection (may give SC or via continuous IV infusion)	Naloxone (0.2–2 mg IV; may repeat in 2–3 min, not to exceed 10 mg)	Respiratory depression, apnea, hypotension, oversedation, nausea or vomiting, constipation, cardiac dysrhythmia, headache, pruritus
Morphine	1–4 mg IV OR IM up to every 5 min	Doses >6 mg rarely needed unless chronic opioid user	Onset: 5–10 min Duration: 4 h	$t_{1/2}$: 2–4 h	Hepatic	IV injection (may give IM, SC, or via continuous IV infusion)		Respiratory depression, anaphylaxis, hypotension, agitation, oversedation, nausea or vomiting, urinary retention, constipation, xerostomia, pruritus, blurry vision

IM, Intramuscular; IV, intravenous; SC, subcutaneous; $t_{1/2}$, half-life.

TABLE 4.8 Overview of Commonly Used Parenteral Anti-arrhythmic Medications in Cardiac Catheterization

ANTIARRHYTHMIC MEDICATIONS	DOSE		DRUG KINETICS AND METABOLISM	ADVERSE EFFECTS	ROUTES OF ADMINISTRATION
	INITIAL	MAXIMUM			
Amiodarone	Pulseless VT or VF: 300-mg IV bolus; if refractory, administer additional 150-mg bolus Stable VT or AF: 150 mg IV piggyback; then start maintenance infusion Maintenance: 1 mg/min for 6 h followed by 0.5 mg/min for 18 h; then transition to PO regimen	2.2 g over 24 h	$t_{1/2}$: 40–55 d (range, 26–107 d)	Hepatic, biliary (minor)	IV
Lidocaine	Pulseless VT or VF if amiodarone is not available: 1–1.5 mg/kg; if refractory, repeat 0.5–0.75 mg/kg every 5–10 min Maintenance: 1–4 mg/min; if hepatic dysfunction, HF, or low muscle mass, then 1–2 mg/min	3 mg/kg	$t_{1/2}$: initially 7–30 min in distribution phase; then 1.5–2 h Onset rapid if given IV with duration of 10–20 min	Hepatic, plasma	CNS side effects (e.g., nystagmus, seizure, tremor), cardiac dysrhythmia, articular chondrolysis, loss of consciousness, methemoglobinemia IV, IO, or endotracheal

AF, Atrial fibrillation; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; CNS, central nervous system; IM, intramuscular; IO, intra-osseous; IV, intravenous; PO, oral; $t_{1/2}$, half-life; VF, ventricular fibrillation; VT, ventricular tachycardia.

few medications from each class, develop deep knowledge about them, and consistently use them. Physicians and staff members should know the intricacies related to the drugs they use, including the evidence, indications, dosages, onsets, and durations of action; reversal, drug–drug interactions; excretion and metabolism; need for dose adjustment among patients with renal or hepatic failure; and side effects (including rare ones). Protocols for commonly used therapies should be written and consistently implemented. Finally, it is important that physicians are mindful of the cost of therapies and their overall value to patients' care and the catheterization laboratory in the contemporary environment of constrained resources.

REFERENCES

- Capodanno D, Ferreiro JL, Angiolillo DJ. Antiplatelet therapy: new pharmacological agents and changing paradigms. *J Thromb Haemost*. 2013; 11(suppl 1):316-329.
- Dorsam RT, Kunapuli SP. Central role of the P2Y₁₂ receptor in platelet activation. *J Clin Invest*. 2004;113(3):340-345.
- Jneid H, Bhatt DL, Corti R, et al. Aspirin and clopidogrel in acute coronary syndromes: therapeutic insights from the CURE study. *Arch Intern Med*. 2003;163(10):1145-1153.
- Angiolillo DJ, Ferreiro JL. Antiplatelet and anticoagulant therapy for atherothrombotic disease: the role of current and emerging agents. *Am J Cardiovasc Drugs*. 2013;13(4):233-250.
- Leger AJ, Covic L, Kuliopulos A. Protease-activated receptors in cardiovascular diseases. *Circulation*. 2006;114(10):1070-1077.
- Jneid H, Bhatt DL. Advances in antiplatelet therapy. *Expert Opin Emerg Drugs*. 2003;8(2):349-363.
- Patrignani P, Filabozzi P, Patrono C. Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. *J Clin Invest*. 1982;69(6):1366-1372.
- Kelly JP, Kaufman DW, Jurgelson JM, et al. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet*. 1996;348(9039):1413-1416.
- Antithrombotic Trialists C. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324(7329):71-86.
- Jolly SS, Pogue J, Haladyn K, et al. Effects of aspirin dose on ischaemic events and bleeding after percutaneous coronary intervention: insights from the PCI-CURE study. *Eur Heart J*. 2009;30(8):900-907.
- Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol*. 2016;68(10):1082-1115.
- Jones WS, Mulder H, Wruck LM, et al. ADAPTABLE Team. Comparative effectiveness of aspirin dosing in cardiovascular disease. *N Engl J Med*. 2021;384(21):1981-1990.
- Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358(9281):527-533.
- Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381(21):2032-2042.
- Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med*. 1996;334(17):1084-1089.
- Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three anti-thrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med*. 1998;339(23):1665-1671.
- Bhatt DL, Bertrand ME, Berger PB, et al. Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting. *J Am Coll Cardiol*. 2002;39(1):9-14.
- Moussa I, Oetgen M, Roubin G, et al. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. *Circulation*. 1999;99(18):2364-2366.
- Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. *Circulation*. 2001;104(5):539-543.
- Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288(19):2411-2420.
- Sabatine MS, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA*. 2005;294(10):1224-1232.
- Depta JP, Bhatt DL. Aspirin and platelet adenosine diphosphate receptor antagonists in acute coronary syndromes and percutaneous coronary intervention: role in therapy and strategies to overcome resistance. *Am J Cardiovasc Drugs*. 2008;8(2):91-112.
- Tantray US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol*. 2013;62(24):2261-2273.
- Mehta SR, Tanguay JF, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet*. 2010;376(9748):1233-1243.
- Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing

- the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2012;60(7):645-681.
26. CURRENT-OASIS Investigators, Mehta SR, Bassand JP, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med*. 2010;363(10):930-942.
 27. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA*. 2011;305(11):1097-1105.
 28. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. 2010;363(20):1909-1917.
 29. Mega JL, Close SL, Wiwiot SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009;360(4):354-362.
 30. Pereira NL, Rihal C, Lennon R, et al. Effect of CYP2C19 genotype on ischemic outcomes during oral p2y12 inhibitor therapy: a meta-analysis. *JACC Cardiovasc Interv*. 2021;14(7):739-750.
 31. Niitsu Y, Jakubowski JA, Sugidachi A, et al. Pharmacology of CS-747 (prasugrel, LY640315), a novel, potent antiplatelet agent with in vivo P2Y12 receptor antagonist activity. *Semin Thromb Hemost*. 2005;31(2):184-194.
 32. Wiwiot SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015.
 33. Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med*. 2012;367(14):1297-1309.
 34. Michelson AD, Frelinger AL III, Braunwald E, et al. Pharmacodynamic assessment of platelet inhibition by prasugrel vs. clopidogrel in the TRITON-TIMI 38 trial. *Eur Heart J*. 2009;30(14):1753-1763.
 35. Gurbel PA, Bliden KP, Butler K, et al. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND study. *Circulation*. 2010;121(10):1188-1199.
 36. Fuster V, Bhatt DL, Califf RM, et al. Guided antithrombotic therapy: current status and future research direction: report on a National Heart, Lung and Blood Institute working group. *Circulation*. 2012;126(13):1645-1662.
 37. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2007;50(19):1852-1856.
 38. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057.
 39. Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2011;124(5):544-554.
 40. James S, Budaj A, Aylward P, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2010;122(11):1056-1067.
 41. Basra SS, Tsai P, Lakkis NM. Safety and efficacy of antiplatelet and antithrombotic therapy in acute coronary syndrome patients with chronic kidney disease. *J Am Coll Cardiol*. 2011;58(22):2263-2269.
 42. Yeh RW, Secemsky EA, Kereiakes DJ, et al. DAPT Study Investigators. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315(16):1735-1749.
 43. Bonaca MP, Bhatt DL, Cohen M, et al. PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372(19):1791-1800.
 44. Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA*. 2013;310(23):2510-2522.
 45. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;130(24):2215-2245.
 46. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64(24):e139-e228.
 47. Schüpke S, Neumann FJ, Menichelli M, et al. ISAR-REACT 5 Trial Investigators. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med*. 2019;381(16):1524-1534.
 48. Jneid H. Ticagrelor or prasugrel in acute coronary syndromes—the winner takes it all? *N Engl J Med*. 2019;381(16):1582-1585.
 49. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362-e425.
 50. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497):1607-1621.
 51. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2011;58(24):e123-e210.
 52. Lopes RD, Heizer G, Aronson R, et al. AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. 2019;380(16):1509-1524.
 53. Kamran H, Jneid H, Kayani WT, et al. Oral antiplatelet therapy after acute coronary syndrome: a review. *JAMA*. 2021;325(15):1545-1555.
 54. Yousuf O, Bhatt DL. The evolution of antiplatelet therapy in cardiovascular disease. *Nat Rev Cardiol*. 2011;8(10):547-559.
 55. Topol EJ, Califf RM, Weisman HF, et al. Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. The EPIC Investigators. *Lancet*. 1994;343(8902):881-886.
 56. EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med*. 1997;336(24):1689-1696.
 57. EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet*. 1998;352(9122):87-92.
 58. Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. *N Engl J Med*. 1999;340(21):1623-1629.
 59. ESPRIT Investigators. Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet*. 2000;356(9247):2037-2044.
 60. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA*. 2006;295(13):1531-1538.
 61. Ellis SG, Tendera M, de Belder MA, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med*. 2008;358(21):2205-2217.
 62. Mehilli J, Kastrati A, Schulz S, et al. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation*. 2009;119(14):1933-1940.
 63. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. *Eur Heart J*. 2009;30(22):2705-2713.
 64. Kastrati A, Mehilli J, Schuhlen H, et al. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med*. 2004;350(3):232-238.
 65. Roffi M, Mukherjee D, Chew DP, et al. Lack of benefit from intravenous platelet glycoprotein IIb/IIIa receptor inhibition as adjunctive treatment for percutaneous interventions of aortocoronary bypass grafts: a pooled analysis of five randomized clinical trials. *Circulation*. 2002;106(24):3063-3067.
 66. Gilchrist IC, O'Shea JC, Kosoglou T, et al. Pharmacodynamics and pharmacokinetics of higher-dose, double-bolus eptifibatide in percutaneous coronary intervention. *Circulation*. 2001;104(4):406-411.
 67. Danzi GB, Capuano C, Sesana M, et al. Variability in extent of platelet function inhibition after administration of optimal dose of glycoprotein IIb/IIIa receptor blockers in patients undergoing a high-risk percutaneous coronary intervention. *Am J Cardiol*. 2006;97(4):489-493.
 68. Hess CN, Schulte PJ, Newby LK, et al. Duration of eptifibatide infusion after percutaneous coronary intervention and outcomes among high-risk patients with non-ST-segment elevation acute coronary syndrome: insights from EARLY ACS. *Eur Heart J Acute Cardiovasc Care*. 2013;2(3):246-255.
 69. Fung AY, Saw J, Starovoytov A, et al. Abbreviated infusion of eptifibatide after successful coronary intervention: the BRIEF-PCI (Brief Infusion of Eptifibatide Following Percutaneous Coronary Intervention) randomized trial. *J Am Coll Cardiol*. 2009;53(10):837-845.
 70. Ellis SG, Tendera M, de Belder MA, et al. 1-year survival in a randomized trial of facilitated reperfusion: results from the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial. *JACC Cardiovasc Interv*. 2009;2(10):909-916.
 71. Giugliano RP, White JA, Bode C, et al. Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med*. 2009;360(21):2176-2190.
 72. Gurm HS, Tamhane U, Meier P, et al. A comparison of abciximab and small-molecule glycoprotein IIb/IIIa inhibitors in patients undergoing primary percutaneous coronary intervention: a meta-analysis of contemporary randomized controlled trials. *Circ Cardiovasc Interv*. 2009;2(3):230-236.
 73. De Luca G, Ucci G, Cassetti E, et al. Benefits from small molecule administration as compared with abciximab among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-analysis. *J Am Coll Cardiol*. 2009;53(18):1668-1673.
 74. Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med*. 2009;361(24):2318-2329.
 75. Bhatt DL, Lincoff AM, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med*. 2009;361(24):2330-2341.
 76. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313.
 77. Steg PG, Bhatt DL, Hamm CW, et al. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. *Lancet*. 2013;382(9909):1981-1992.
 78. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes

- (RIVAL): a randomised, parallel group, multicentre trial. *Lancet*. 2011; 377(9775):1409-1420.
79. Doherty TM, Shavelle RM, French WJ. Reproducibility and variability of activated clotting time measurements in the cardiac catheterization laboratory. *Catheter Cardiovasc Interv*. 2005;65(3):330-337.
 80. Chew DP, Bhatt DL, Lincoff AM, et al. Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. *Circulation*. 2001;103(7):961-966.
 81. Warkentin TE. Drug-induced immune-mediated thrombocytopenia-from purpura to thrombosis. *N Engl J Med*. 2007;356(9):891-893.
 82. Ferguson JJ, Califf RM, Antman EM, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA*. 2004;292(1):45-54.
 83. Martin JL, Fry ET, Sanderink GJ, et al. Reliable anticoagulation with enoxaparin in patients undergoing percutaneous coronary intervention: the pharmacokinetics of enoxaparin in PCI (PEPCI) study. *Catheter Cardiovasc Interv*. 2004;61(2):163-170.
 84. Gibson CM, Murphy SA, Montalescot G, et al. Percutaneous coronary intervention in patients receiving enoxaparin or unfractionated heparin after fibrinolytic therapy for ST-segment elevation myocardial infarction in the EXTRACT-TIMI 25 trial. *J Am Coll Cardiol*. 2007;49(23):2238-2246.
 85. Montalescot G, Gallo R, White HD, et al. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention 1-year results from the STEEPLE (SafeTy and efficacy of enoxaparin in percutaneous coronary intervention patients, an international randomized evaluation) trial. *JACC Cardiovasc Interv*. 2009;2(11):1083-1091.
 86. Montalescot G, Ellis SG, de Belder MA, et al. Enoxaparin in primary and facilitated percutaneous coronary intervention: a formal prospective non-randomized substudy of the FINESSE trial (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events). *JACC Cardiovasc Interv*. 2010;3(2):203-212.
 87. Brieger D, Collet JP, Silvain J, et al. Heparin or enoxaparin anticoagulation for primary percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2011;77(2):182-190.
 88. Dumaine R, Borentain M, Bertel O, et al. Intravenous low-molecular-weight heparins compared with unfractionated heparin in percutaneous coronary intervention: quantitative review of randomized trials. *Arch Intern Med*. 2007;167(22):2423-2430.
 89. Cohen M, Levine GN, Pieper KS, et al. Enoxaparin 0.3 mg/kg IV supplement for patients transitioning to PCI after subcutaneous enoxaparin therapy for NSTEMI ACS: a subgroup analysis from the SYNERGY trial. *Catheter Cardiovasc Interv*. 2010;75(6):928-935.
 90. Montalescot G, White HD, Gallo R, et al. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. *N Engl J Med*. 2006;355(10):1006-1017.
 91. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA*. 2003;289(7):853-863.
 92. Lincoff AM, Kleiman NS, Kereiakes DJ, et al. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA*. 2004;292(6):696-703.
 93. Schulz S, Mehili J, Ndrepepa G, et al. Bivalirudin vs. unfractionated heparin during percutaneous coronary interventions in patients with stable and unstable angina pectoris: 1-year results of the ISAR-REACT 3 trial. *Eur Heart J*. 2010;31(5):582-587.
 94. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med*. 2006;355(21):2203-2216.
 95. Stone GW, Witzencbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358(21):2218-2230.
 96. Stone GW, Clayton T, Dellagryis EN, et al. Reduction in cardiac mortality with bivalirudin in patients with and without major bleeding: the HORIZONS-AMI trial (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction). *J Am Coll Cardiol*. 2014;63(1):15-20.
 97. Steg PG, van 't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med*. 2013;369(23):2207-2217.
 98. Dangas G, Mehran R, Guagliumi G, et al. Role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty: results from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. *J Am Coll Cardiol*. 2009;54(15):1438-1446.
 99. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet*. 2014;384(9957):1849-1858.
 100. Berger PB, Blankenship JC. Is the heat on HEAT-PPCI appropriate? *Lancet*. 2014;384(9957):1824-1826.
 101. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med*. 2006;354(14):1464-1476.
 102. Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA*. 2006;295(13):1519-1530.
 103. Dhillon S. Argatroban: a review of its use in the management of heparin-induced thrombocytopenia. *Am J Cardiovasc Drugs*. 2009;9(4):261-282.
 104. Rezkalla SH, Dharmashankar KC, Abdalrahman IB, et al. No-reflow phenomenon following percutaneous coronary intervention for acute myocardial infarction: incidence, outcome, and effect of pharmacologic therapy. *J Interv Cardiol*. 2010;23(5):429-436.
 105. Bruder O, Breuckmann F, Jensen C, et al. Prognostic impact of contrast-enhanced CMR early after acute ST segment elevation myocardial infarction (STEMI) in a regional STEMI network: results of the "Herzinfarktverbund Essen." *Herz*. 2008;33(2):136-142.
 106. Fischell TA, Carter AJ, Foster MT, et al. Reversal of "no reflow" during vein graft stenting using high velocity boluses of intracoronary adenosine. *Catheter Cardiovasc Diagn*. 1998;45(4):360-365.
 107. Stoeil MG, Marques KM, de Cock CC, et al. High dose adenosine for suboptimal myocardial reperfusion after primary PCI: a randomized placebo-controlled pilot study. *Catheter Cardiovasc Interv*. 2008;71(3):283-289.
 108. Navarese EP, Buffon A, Andreotti F, et al. Adenosine improves post-procedural coronary flow but not clinical outcomes in patients with acute coronary syndrome: a meta-analysis of randomized trials. *Atherosclerosis*. 2012; 222(1):1-7.
 109. Jeremias A, Whitbourn RJ, Filardo SD, et al. Adequacy of intracoronary versus intravenous adenosine-induced maximal coronary hyperemia for fractional flow reserve measurements. *Am Heart J*. 2000;140(4):651-657.
 110. Leone AM, Porto I, De Caterina AR, et al. Maximal hyperemia in the assessment of fractional flow reserve: intracoronary adenosine versus intracoronary sodium nitroprusside versus intravenous adenosine: the NASCI (Nitroprussiato versus Adenosina nelle Stenosi Coronariche Intermedie) study. *JACC Cardiovasc Interv*. 2012;5(4):402-408.
 111. Hillegass WB, Dean NA, Liao L, et al. Treatment of no-reflow and impaired flow with the nitric oxide donor nitroprusside following percutaneous coronary interventions: initial human clinical experience. *J Am Coll Cardiol*. 2001;37(5):1335-1343.
 112. Wang HJ, Lo PH, Lin JJ, et al. Treatment of slow/no-reflow phenomenon with intracoronary nitroprusside injection in primary coronary intervention for acute myocardial infarction. *Catheter Cardiovasc Interv*. 2004; 63(2):171-176.
 113. Jaffe R, Dick A, Strauss BH. Prevention and treatment of microvascular obstruction-related myocardial injury and coronary no-reflow following percutaneous coronary intervention: a systematic approach. *JACC Cardiovasc Interv*. 2010;3(7):695-704.
 114. Su Q, Li L, Naing KA, et al. Safety and effectiveness of nitroprusside in preventing no-reflow during percutaneous coronary intervention: a systematic review. *Cell Biochem Biophys*. 2014;68(1):201-206.
 115. Huang RI, Patel P, Walinsky P, et al. Efficacy of intracoronary nicardipine in the treatment of no-reflow during percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2006;68(5):671-676.
 116. Hang CL, Wang CP, Yip HK, et al. Early administration of intracoronary verapamil improves myocardial perfusion during percutaneous coronary interventions for acute myocardial infarction. *Chest*. 2005;128(4):2593-2598.
 117. Huang D, Qian J, Ge L, et al. REStoration of COronary flow in patients with no-reflow after primary coronary interVENTion of acute myocArdial infarction (RECOVER). *Am Heart J*. 2012;164(3):394-401.
 118. Krumholz HM, Anderson JL, Bachelder BL, et al. ACC/AHA 2008 performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to develop performance measures for ST-elevation and non-ST-elevation myocardial infarction): developed in collaboration with the American Academy of Family Physicians and the American College of Emergency Physicians: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Society for Cardiovascular Angiography and Interventions, and Society of Hospital Medicine. *Circulation*. 2008;118(24): 2596-2648.
 119. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497):1622-1632.
 120. McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation*. 2008;117(14):1897-1907.
 121. Francis GS, Bartos JA, Adaya S. Inotropes. *J Am Coll Cardiol*. 2014;63(20): 2069-2078.
 122. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9): 779-789.
 123. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology*. 2002;96(4):1004-1017.
 124. Levine JH, Massumi A, Scheinman MM, et al. Intravenous amiodarone for recurrent sustained hypotensive ventricular tachyarrhythmias. Intravenous Amiodarone Multicenter Trial Group. *J Am Coll Cardiol*. 1996;27(1):67-75.
 125. Dorian P, Cass D, Schwartz B, et al. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med*. 2002;346(12): 884-890.



5 Hemodynamic Support During High-Risk Percutaneous Coronary Intervention

WILLIAM W. O'NEILL AND BRIAN O'NEILL P

INTRODUCTION, 80

RATIONALE FOR DEFINITION OF "HIGH RISK", 80

CLINICAL PRESENTATION, 81

CORONARY BLOOD FLOW AND MYOCARDIAL ENERGETICS DURING HIGH-RISK PERCUTANEOUS CORONARY INTERVENTION, 81

EXTRACORPOREAL MEMBRANE OXYGENATION, 84

HISTORY OF DEVELOPMENT OF LEFT VENTRICULAR SUPPORT DEVICES FOR HR PERCUTANEOUS CORONARY INTERVENTION, 86

HISTORY OF USE OF INTRA-AORTIC BALLOON PUMP DURING HIGH-RISK PERCUTANEOUS CORONARY INTERVENTION, 86

BALLOON-PUMP ASSISTED CORONARY INTERVENTION STUDY, 87

HISTORY OF TANDEMHEART DEVELOPMENT, 88

TRANSVALVULAR AXIAL FLOW PUMPS, 89

HISTORY OF IMPELLA DEVELOPMENT, 89

CLINICAL TRIALS OF IMPELLA IN HIGH-RISK PERCUTANEOUS CORONARY INTERVENTION, 91

PROTECT II, 91

OPTIMAL USE OF IMPELLA FOR HEMODYNAMIC SUPPORT, 95

CASE EXAMPLE, 96

COMPLICATIONS OF IMPELLA, 97

CONCLUSION: FUTURE ADVANCES, 98

INTRODUCTION

Coronary balloon angioplasty (percutaneous transluminal coronary angioplasty [PTCA]), introduced in 1977,¹ was initially limited to treatment of focal, noncalcified, proximal, concentric coronary lesions. Initially, case selection was confined to patients with normal left ventricular (LV) function and single-vessel coronary artery disease (CAD).² Complex lesions (eccentric, bifurcation, chronic total occlusion [CTO]) and patients with multivessel coronary disease simply could not be technically approached. Dramatic advances in guidewire technology; advances in balloon technology; new atherectomy devices; and the introduction of flexible, easily deployable stents have dramatically expanded the complexity of the lesions that can be treated successfully. As the age of the population and the life expectancy of patients with overt CAD increase, clinicians are increasingly faced with older, highly symptomatic patients with multiple comorbidities that make percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) prohibitively risky. In this setting, the coronary interventionalist is asked to perform a PCI. To safely undertake these high-risk procedures, hemodynamic support may be required. Which patients require hemodynamic support and what method of support is safest and most effective are the subjects of this chapter.

RATIONALE FOR DEFINITION OF "HIGH RISK"

Through the 1990s and up until 2005, scores of studies were published regarding "high-risk" percutaneous coronary

intervention (HRPCI).³ Most studies were single-center registries or a few prospective multicenter registries.⁴⁻⁶ Wide variations in outcomes were reported. The consistent characteristic that appeared to enhance risk was severely impaired ventricular function.

Keelan et al.⁷ have demonstrated a 30-fold increase in risk of death for patients with ejection fractions (EFs) less than 40% compared with patients with normal EFs. There are multiple reasons why underlying impaired LV function increases risk. First, to have EFs less than 40%, patients have survived an extensive acute myocardial infarction (MI). This often results in the presence of a CTO. As survivors of acute MI, these patients present later with recurrent symptoms related to worsening of another coronary artery. Thus, patients are later into the natural history of their disease and usually have multiple-vessel disease. As patients with CAD age, other comorbidities such as diabetes, chronic kidney disease (CKD), and chronic obstructive lung disease increase the procedural risk. During the interventional procedure, patients with severely depressed LV function pose a special challenge. Typically, the operator is treating a stenosis that subtends a large segment of the normally contracting left ventricle and that often subtends a distant myocardial segment that has blood flow through the collaterals. Repeated interruptions of blood flow that occur with contrast injections, balloon inflation, and stent manipulation can lead to ischemia of normally contracting myocardial segments. This results in marked elevation of LV filling pressure and can quickly lead to sustained hypotension or cardiovascular collapse. For this reason, the two main prospective randomized trials, hemodynamic support with Impella 2.5 versus the intra-aortic

balloon pump (IABP)⁸ and the balloon pump-assisted Coronary Intervention Study,⁹ have both used severely impaired LV function as the primary risk segregator. In addition, the Balloon-Pump Assisted Coronary Intervention Study (BCIS) investigators chose an advanced jeopardy score of 8 or greater (of 12), and the PROTECT II investigators added the presence of a last patent coronary vessel as an inclusion criterion (Table 5.1). These simple, concise criteria have defined a patient population with a 30-fold increase in mortality risk during hospitalization compared with routine elective multiple vessel angioplasty (Table 5.2). One new major randomized trial, PROTECT IV (Clintrial.gov

04763200) is also now using left ventricular ejection fraction (LVEF) of 40% or less as the primary risk segregator.

CLINICAL PRESENTATION

This chapter initially discusses management of elective or urgent patients who are treated outside the setting of acute MI or cardiogenic shock. These patients present late in the natural history of coronary atherosclerosis. Their average age is older than 70 years. A large proportion of the population has diabetes mellitus, their renal function is impaired, and they are highly symptomatic. New York Heart Association (NYHA) III or IV symptoms were present in 60% of the patients in the BCIS and 65% of those in PROTECT II. Symptoms could be worsening heart failure or angina. In fact, because a large segment of these patients have diabetes, it is often difficult to differentiate worsening heart failure from worsening ischemia. In the PROTECT II study, 26% of the patients had peripheral vascular disease, and 64% were evaluated and turned down for CABG by the site surgeons. Thus, these older, highly symptomatic patients have limited therapeutic options apart from HRPPI. Age, poor ventricular function, diabetes, CKD, and peripheral vascular disease all increase procedural risk. In addition, coronary angiography, intravascular ultrasound (IVUS) interrogation, coronary balloon inflation, intravascular lithotripsy, rotational atherectomy, or complex stent procedures (kiss, crush, culotte) may compromise coronary blood flow to the vital myocardial segments. Without hemodynamic support, these coronary manipulations can result in cardiovascular collapse. To avoid cardiac collapse, clinicians may choose to perform unassisted procedures with minimal coronary angiography, lack of IVUS interrogation, brief balloon use, stent inflation, and incomplete revascularization. Even with these precautions, in the BCIS study, 10% of the control (unsupported patients) had severe hypotension, and 12% of the patients required rescue IABP. To optimize patient safety and long-term clinical effectiveness, a controlled, well-planned, supported PCI procedure must be considered.

CORONARY BLOOD FLOW AND MYOCARDIAL ENERGETICS DURING HIGH-RISK PERCUTANEOUS CORONARY INTERVENTION

Coronary blood flow physiology is well defined in mammalian models (Figure 5.1).¹⁰ It is known that under conditions of maximal stress, a fourfold increase in resting blood flow can occur. Coronary occlusions begin to impact vasodilator reserve at 50% area occlusion and eliminate vasodilator capacity at 80% occlusion. After this, resting coronary blood flow dramatically decreases with small increases in occlusion severity. It is also well understood that in mammals, a perfusion gradient of 30 to 50 mm Hg is required to drive blood through the myocardium (Figure 5.2).¹¹ In systole, when aortic and ventricular pressures are the same and when ventricular compression occurs, little forward blood flow occurs. Thus, mammalian coronary blood flow is largely diastolic. As coronary occlusion worsens,

TABLE 5.1 Definition of High-Risk Percutaneous Coronary Intervention

	BCIS	PROTECT II
Inclusion criteria ^b	PCI native vessel or SVBG LVEF ≤30% on echocardiogram Jeopardy score ≥8 of 12	PCI native vessel or SVBG PCI last patent vessel LVEF ≤30% with three VD ^a LVEF ≤35% with UPLM
Exclusion criteria	Acute MI or shock Acute VSD or MR More than mild AR on echocardiogram Planned staged procedure	Acute MI or shock Acute VSD or MR LV thrombus on echo Creatinine ≥3 mg/dl AS with AVA ≤1.5 cm ²

^aJeopardy score (Modified Duke Jeopardy score, which allows subclavian and left main lesions).

^bIn comparison with SYNTAX, BCIS, and PROTECT II, trials treated older patients with impaired left ventricular function who have more after a history of coronary artery bypass grafting (CABG) or prior myocardial infarction (MI). Major adverse cardiovascular events continued to increase between 30 and 90 days.

^cIn PROTECT II, 66% of patients were formally turned down for surgery by site surgeons. It is not known if the remaining 32% were ever evaluated for CABG.⁸ AR, Aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; SVBG, saphenous vein bypass graft; UPLM, unprotected left main; VD, vessel disease; VSD, ventricular septal defect.

TABLE 5.2 Baseline Characteristics and Outcome

	BCIS, PROTECT II, AND SYNTAX TRIALS		
	SYNTAX	BCIS	PROTECT II
Age (y)	65 ± 10	71 ± 10	68 ± 10
History of CHF (%)	NR	6	87
History of CABG (%)	0	15	33
Prior MI (%)	32	73	68
SYNTAX score (mean)	28	32	30
LVEF ≤35%	2.3%	100%	95%
LMCA PCI (%)	39	27	22
Surgery candidate	100%	NR	<32% ^a
30-day death (%)	2	2	7.6
90-day death (%)	3	5	10
30-day MACE (%)	6	15	10
90-day MACE (%)	15	NR	22

^aA total of 68% of patients in PROTECT II had formal denial of surgical candidacy by site surgeon.

BCIS, Balloon-Pump Assisted Coronary Intervention Study; CABG, coronary artery bypass; CHF, congestive heart failure; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention. From Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-972.

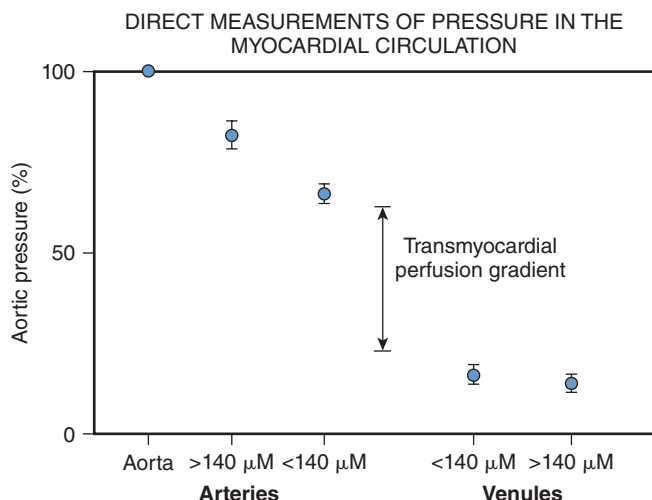


FIGURE 5.1 Myocardial perfusion. Using a micropuncture technique demonstrated the contribution of arterial and venous vessels to vascular pressure in the left ventricle. The vast majority of pressure decreases occur between small-caliber arteries and vessels. Coronary sinus (or right atrial pressure) contributes little to the perfusion gradient. Assuming a left ventricular end-diastolic pressure of 10 mm Hg, a minimum aortic diastolic pressure of 40 mm Hg is needed to ensure antegrade transmural blood flow. (Adapted with permission from Marcus ML. *The Coronary Circulation in Health and Disease*. McGraw-Hill; 1983.)

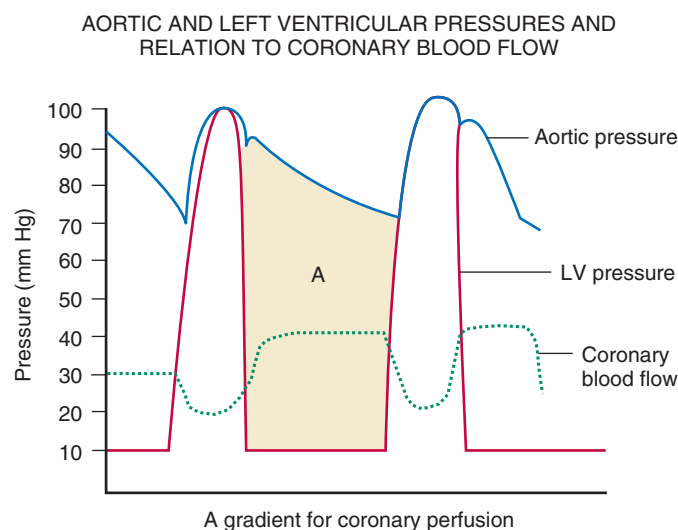


FIGURE 5.2 Coronary blood flow + left ventricular (LV) + aortic pressure. In the absence of severe coronary lesions, coronary blood flow (CBF) is largely diastolic (dotted line). CBF is regulated by coronary arteries that dilate in response to physiologic stimuli. Any factors that decrease the diastolic interval or decrease the diastolic perfusion gradient will diminish CBF. Hypotension lowers diastolic pressures, and ischemia raises left ventricular end-diastolic pressure. These two events occur frequently during high-risk percutaneous coronary intervention and can decrease coronary blood flow to the point of cardiovascular collapse. (Courtesy of Dr. William W. O'Neill.)

the phasic nature diminishes, and blood flow is largely driven by the mean arterial pressure (MAP) with requirement for a gradient of 30 to 50 mm Hg for perfusion. How do these principles translate to this high-risk population? First, generally, all three major coronary territories are affected with severe atherosclerosis. One or more coronaries may be chronically totally occluded from previous infarctions. Patients present with worsening of non-infarct-related vessels with lesions severe enough to diminish

vasodilatory reserve or decrease resting coronary blood flow. The remaining patent vessels provide collateral flow to the occluded territories and likely have severe lesions. The demand for increased coronary blood flow to supply collateral flow and the usual hyperkinesis of the noninfarct zones cause the patent coronaries to be at a maximal state of coronary vasodilation. In this setting, blood flow is entirely driven by perfusion gradient (Figure 5.3).¹⁰ No incremental vasodilation is possible because the patent vessels have severe underlying lesions. Thus, the coronary tree has no capacity for augmentation of blood flow (Figure 5.4). Coronary blood flow is driven entirely by the transmyocardial perfusion gradient and diastolic interval. When patients become distressed, tachycardia, elevated left ventricular end-diastolic pressure (LVEDP), and systolic hypotension occur. These factors dramatically increase myocardial oxygen demand (MVO₂) (Figure 5.5)¹² or decrease supply. At the same time, decreased perfusion gradients and coronary blood flow can lead to a rapid cycle of worsening ischemia and lowering of blood pressure, which leads to less coronary blood flow, worsening myocardial contracture, and irreversible shock. To prevent this catastrophe, measures to maximize the myocardial perfusion gradient, minimize MVO₂, and maintain adequate cardiac output for vital organ perfusion are required.

In addition to coronary blood flow physiology, an understanding of myocardial energetics is required to determine optimal support strategies for these patients. Myocardial energetics can be studied using pressure volume relationships. Suga et al.¹³ and Burkhoff¹⁴ demonstrated that pressure-volume loops are an ideal way to define cardiac performance throughout the cardiac cycle (Figure 5.6). Ideally, interventions that decrease the end-diastolic pressure-volume relationship improve myocardial energetics by decreasing ventricular wall tension and thus decreasing MVO₂. At the same time, interventions that increase the end-systolic pressure-volume relationship increase the

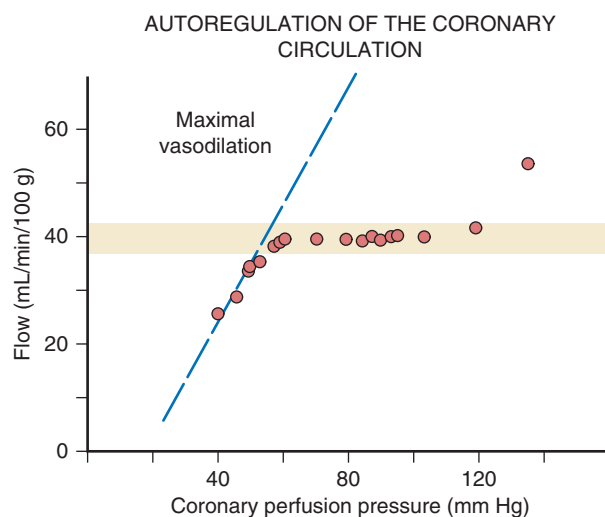


FIGURE 5.3 Maximal flow during vasodilatation. The normal maximal circulation can autoregulate over a wide range of pressures during conditions of maximal dilation. When coronary perfusion pressure drops below 50 mm Hg, a rapid decline in coronary blood flow (CBF) will occur. CBF will cease when perfusion gradients less than 20 mm Hg occur. (Adapted with permission from Marcus ML. *The Coronary Circulation in Health and Disease*. McGraw-Hill; 1983.)



FIGURE 5.4 Factors impacting coronary blood flow during high-risk percutaneous coronary intervention (PCI). Clinicians face an uphill battle during high-risk PCI. They have limited means to maintain or improve coronary blood flow (CBF) while faced with numerous factors that tend to decrease or abolish CBF during intervention. *LVEDP*, Left ventricular end-diastolic pressure.

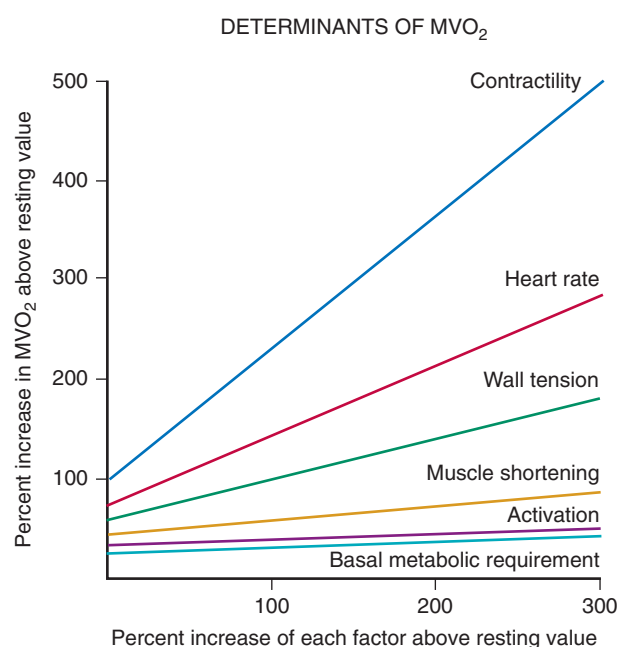


FIGURE 5.5 Factors increasing myocardial oxygen demand (MVO_2). An ideal support strategy for high-risk percutaneous coronary intervention (HRPCI) should rest the left ventricle so that contractility, wall tension, and perhaps heart rate could be decreased, thereby decreasing MVO_2 . Conversely, during HRPCI, the use of inotropes may increase systolic pressure but at the expense of an increase in MVO_2 . This sets up a supply–demand mismatch. (Adapted with permission from Marcus ML. *The Coronary Circulation in Health and Disease*. McGraw-Hill; 1983.)

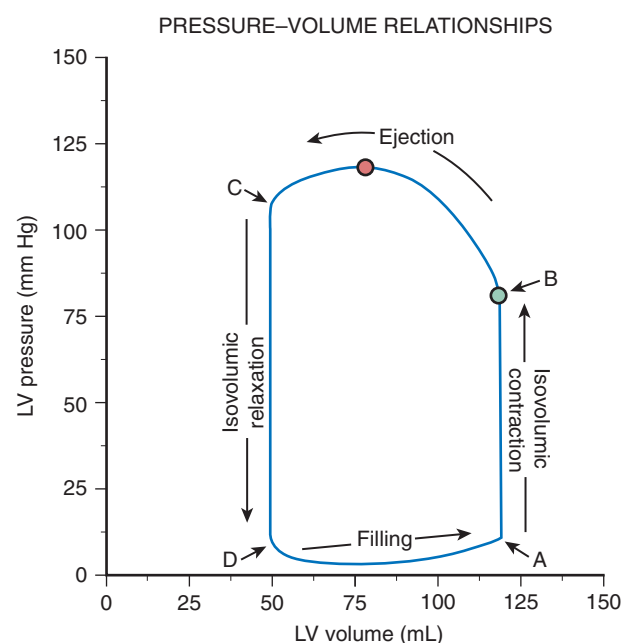


FIGURE 5.6 Pressure–volume relationships. The science of hemodynamic support and catheterization cardiology intervention.¹⁴ Diastolic and systolic compliance is best considered at end-diastole and systolic contractility at end-systole. To optimize cardiac performance, left ventricular end-diastolic pressure decrease and left ventricular end-systolic pressure increase are required. (Reproduced with permission from Burkhoff D, Naidu SS. The science behind percutaneous hemodynamic support: a review and comparison of support strategies. *Cathet Cardiovasc Interv*. 2012;80(5):816-829.)

transmyocardial perfusion gradient and improve coronary blood flow. When the transmyocardial pressure gradient drops below 30 mm Hg because of a decrease in MAP or an elevation of LVEDP, dangerous reductions in coronary blood flow occurs, and cardiac collapse soon follows. Thus, the goal of hemodynamic support is threefold. First, maintaining a MAP of 60 mm Hg or greater is required to maintain coronary flow. Second, maintaining a cardiac power of 0.6 or greater watts prevents systemic hypoperfusion.¹⁵ Finally, decreasing ventricular diastolic pressure enhances the coronary perfusion gradient and decreases LV wall tension. Burkhoff and Naidu¹⁶ summarized the impact of hemodynamic support strategies on these three variables using a circulation simulator.

Each hemodynamic support maneuver has been modeled (Figure 5.7). First, inotropic agents appear to augment

MAP and cardiac output but do so at the expense of increasing diastolic filling pressure (pulmonary capillary wedge pressure [PCWP]) and thus increasing MVO_2 . Inotropes increase MVO_2 by increasing contractility, heart rate, and wall tension. If LVEDP is increased proportionally more than MAP, myocardial perfusion pressure is lowered, and coronary blood flow will drop. At high levels of alpha-adrenergic tone, coronary vasoconstriction will occur, and coronary blood flow will drop further. Thus, use of inotropes alone is a poor strategy that provides only modest support of MAP at the expense of increased MVO_2 and potentially less coronary blood flow.

The addition of an IABP to an inotropic support provides more support of MAP and cardiac output but does so at the expense of elevations of wall tension and MVO_2 . It is likely that the increased MVO_2 demand will not be matched

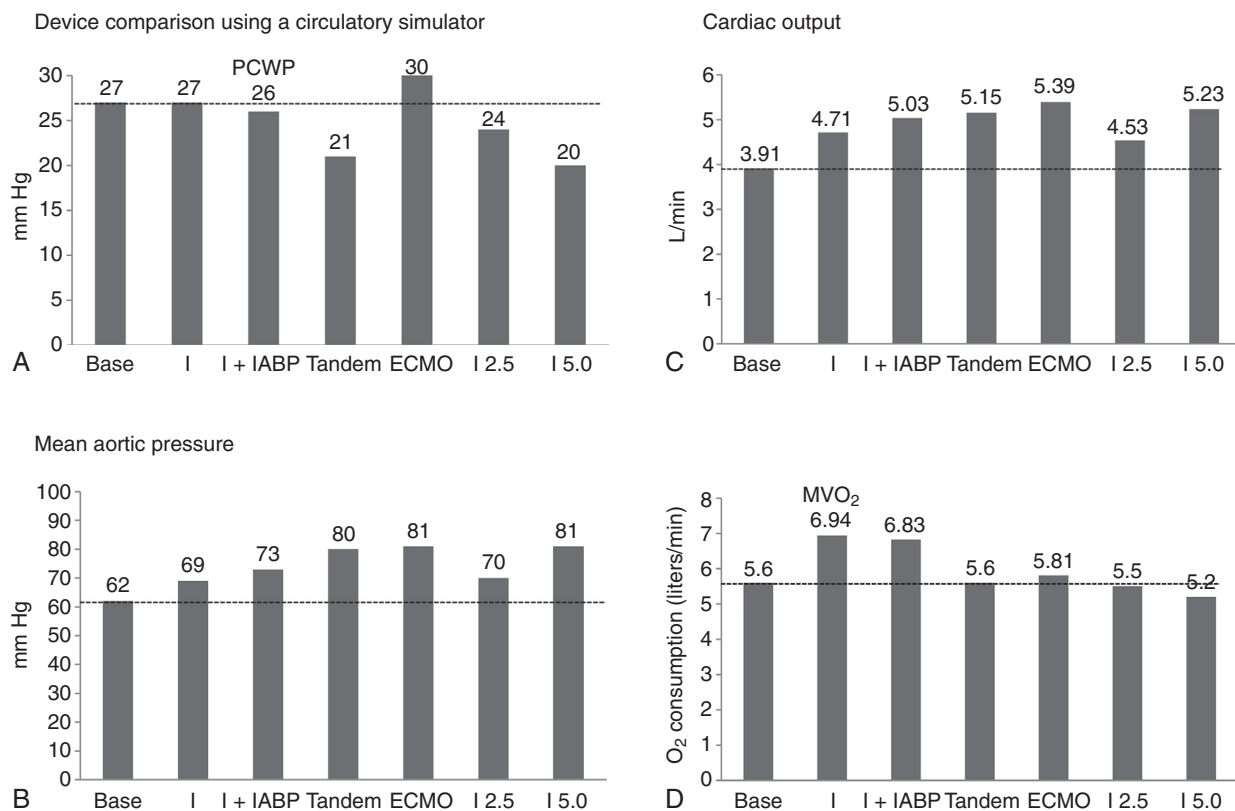


FIGURE 5.7 Modeling. Burkhoff modeled changes in hemodynamics that occur with various support strategies. Pulmonary capillary wedge pressure (PCWP) (A), cardiac output (C), mean aortic pressure (B), and myocardial oxygen consumption changes (D) are calculated. The dotted line is a baseline value, and support strategies can be seen to increase or decrease each parameter. ECMO, Extracorporeal membrane oxygenation; IABP, intraaortic balloon pump; MVO₂, myocardial oxygen demand. (Reproduced with permission from Burkhoff D. Pressure-volume loops in clinical research: a contemporary view. *J Am Coll Cardiol.* 2013;62(13):1173-1176.)

by increased coronary blood flow, and this will set up a substrate for myocardial ischemia. The impact of IABP on coronary blood flow has been of interest for three decades. Soon after its introduction, it became apparent that IABP could stabilize patients with recurrent, medically refractory unstable angina. Williams et al.¹⁷ measured left anterior descending coronary artery (LAD) blood flow by placing thermodilution catheters into the great cardiac vein in six patients with refractory angina who had severe proximal LAD lesions. They found that the greater cardiac vein flow decreased from 78 ± 11 to 69 ± 8 mL/min ($P = .048$) when IABP support was initiated. In addition, systolic pressure was significantly reduced, and augmented diastolic pressure was increased. They concluded that the mechanism of the relief of angina related to the decreased afterload and decreased MVO₂ rather than increased coronary blood flow. Yoshitani et al.¹⁸ measured coronary pressures using the Radi Wire (Radi Medical Systems) in 16 patients with unstable angina. Pressures were measured distal to 16 culprit lesions and 5 normal vessels. The distal diastolic pressures were unchanged after initiation of IABP distal to the severe stenotic segments (42.8 ± 17 to 44 ± 21 ; $p =$ not significant [NS]). In the normal vessels, pressures increased with initiation of IABP (78 ± 9 to 97 ± 8 mm Hg; $P < .05$). Kern et al.^{19,20} measured coronary flow velocity with a Doppler-tipped catheter (Millar Instruments). They found that the coronary flow velocity was unchanged distal to severe lesions after IABP was turned

on. After PTCA of the lesion, coronary flow velocity significantly increased with IABP support. Thus, IABP support may be of benefit when severe hypotension occurs and one or more coronary arteries are free of disease. In this circumstance, augmentation of diastolic pressure will enhance coronary blood flow. Because most patients undergoing HRPPI have multivessel disease, IABP support will be of little value in maintaining or supporting coronary blood flow.

The TandemHeart Pump (LivaNova) substantially decreases filling pressure and augments MAP as well as cardiac output.²¹ Because wall tension is reduced and MAP is elevated, MVO₂ is reduced, and coronary blood flow should be increased. Of the hemodynamic support devices, Impella is the only one that directly drains the left ventricle and augments forward cardiac flow. As cardiac output is increased from 2.5 to 5 L, filling pressures are reduced, MAP is elevated, and the myocardial perfusion gradient is elevated. This device has the ideal properties of maintaining MAP and forward cardiac output while decreasing MVO₂. The device seems well suited for short- and long-term hemodynamic support.

EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO), also known as peripheral cardiopulmonary bypass (CPS), is

unequivocally useful when both right and left heart failure occurs. It provides excellent support for cardiac output and MAP. Unfortunately, it does so at the expense of elevated filling pressure and elevated MVO_2 . For patients with severe multivessel CAD, it is likely that a longer duration of the use of this device sets up a substrate for myocardial ischemia. In the short term, the device provides superb support of the cardiac output and mean aortic pressure.

In patients with severe heart failure, particularly biventricular failure, or extensive CAD, ECMO may be desirable to allow complete hemodynamic support as well as the added benefit of arterial oxygenation during PCI. A large-bore 17- or 19-Fr arterial cannula outflow is required, so ECMO may be contraindicated in patients with peripheral arterial disease. The venous inflow can be delivered through a 22-Fr cannula. The outcomes for patients undergoing PCI with ECMO are largely in the form of registries. A two-hospital study enrolled 14 patients who underwent prophylactic venoarterial (VA) ECMO for HRPCI. A total of 71% of patients had severely impaired LV function ($\text{LVEF} < 35\%$), and the left main coronary artery was the main target vessel in 71% of cases. PCI was successful in 100% of cases, and the rate of survival to hospital discharge was 93%.²² A South Korean study examined patients undergoing PCI after out-of-hospital cardiac arrest (OHCA) supported by VA ECMO. Of 116,375 patients experiencing OHCA, 184 who were resuscitated underwent VA ECMO-supported PCI. Overall, the in-hospital mortality rate was high in the study at 78.8% but lower in the pre-PCI ECMO group.²³ In data from the National Inpatient Sample that compared 5730 patients undergoing PCI with Impella versus 560 who underwent PCI with ECMO, there was a lower rate of vascular complications in the Impella group.²⁴ Finally, the EURO SHOCK trial will randomize 428 patients with cardiogenic shock complicating PCI to early ECMO plus pharmacotherapy versus pharmacotherapy alone. Data from this trial will be available in the coming years. The timing of ECMO implantation, whether before or after PCI, remains an unanswered question.²⁵

To overcome the increase in afterload and increase in LV wall tension of VA ECMO, a new configuration of cannula has been developed called left atrial venous arterial (LAVA) ECMO. In LAVA ECMO, a fenestrated drainage cannula is inserted into the left atrium via transeptal puncture. This cannula has fenestrations that allow drainage of left atrial and right atrial blood. This and mixed blood are sent through a membrane oxygenator and reinserted through a femoral artery. Both left and right ventricles are decompressed, and essentially, biventricular bypass is accomplished.

We have used this configuration in patients with acute MI cardiogenic shock²⁶ and in those with CAD and severe aortic insufficiency.²⁷ A 51-year-old patient presented with severe CAD (Figure 5.8) and massive aortic insufficiency caused by bioprosthetic valve failure with flail leaflets. The patient was placed on LAVA ECMO, and rapid hemodynamic improvement resulted (Figure 5.9). As can be noted on the waveforms, dramatic decrease in left atrial and LVEDP occurred as well as decline in wedge and right atrial pressures. The patient was stabilized and 3 days later

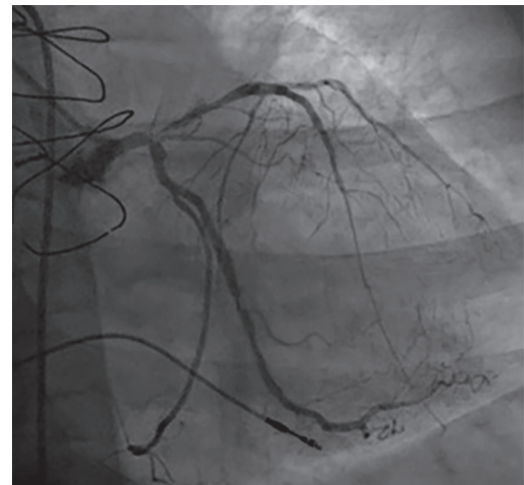


FIGURE 5.8 Coronary angiogram from a 51-year-old patient who presented with severe coronary artery disease and massive aortic insufficiency caused by bioprosthetic valve failure with flail leaflets.

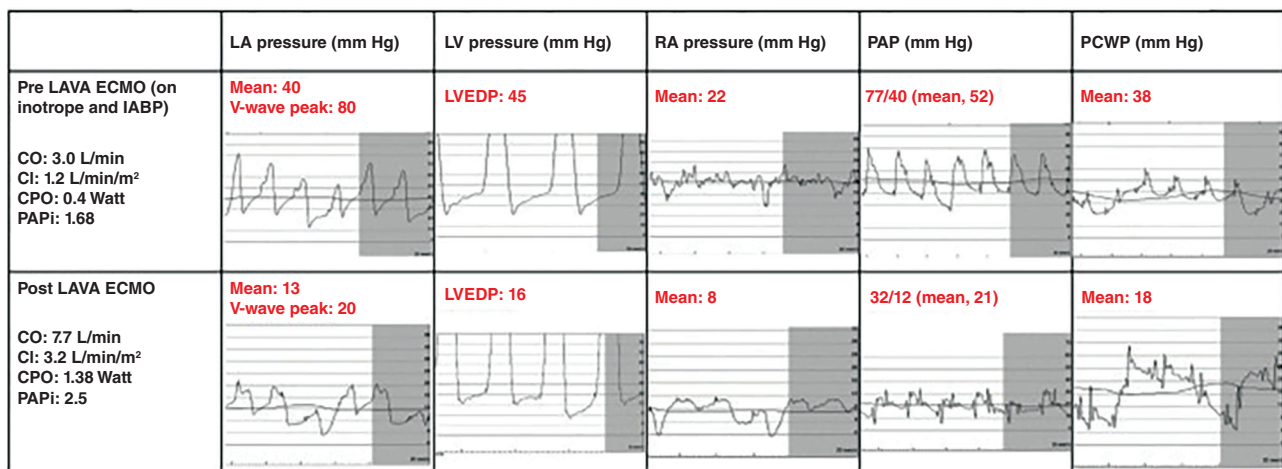


FIGURE 5.9 As can be noted on the wave forms, dramatic decrease in left atrial (LA) and left ventricular (LV) end-diastolic pressure (LVEDP) occurred as well as decline in wedge and right atrial (RA) pressures. CI, Cardiac index; CO, cardiac output; CPO, cardiac power output; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic balloon pump; LAVA, left atrial venous arterial; PAP, pulmonary artery pressure; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; RV, right ventricular.

underwent PCI of ostial LAD and obtuse marginal (OM) lesions while on support. Two days later, the patient underwent a transfemoral transcatheter aortic valve replacement valve-in-valve procedure and recovered with return of EF to normal levels.

This configuration has primary value in providing biventricular support when a prolonged duration of support is anticipated. For patients who are stable before the procedure, biventricular support is not needed. The previous discussion of modeling provides the clinician with the theoretic basis to choose from a variety of support strategies. In addition to these factors, patient body surface area, status of peripheral circulation, urgency of the need for hemodynamic support, and operator training and experience using the individual devices play a major role in defining an optimal support strategy for individual patients. Ideally, these complex interventions should be performed in referral centers with expertise and access to many types of support and with open communication either in house or rapidly available left ventricular assist device (LVAD) and transplant referral support.

HISTORY OF DEVELOPMENT OF LEFT VENTRICULAR SUPPORT DEVICES FOR HIGH-RISK PERCUTANEOUS CORONARY INTERVENTION

The 1985 to 1986 National Heart, Lung, and Blood Institute (NHLBI) registry of coronary angioplasty documented outcomes for PCI in the prestant era.²⁸ The presence of depressed LV function identified a group of patients who often had multivessel CAD. When the LVEF was less than or equal to 35%, there was a 3% mortality rate compared with a 0.1% mortality rate for patients with LVEF greater than 45%. LV support with IABP was first developed to improve outcomes. The IABP had been in use since 1968²⁹ and was widely used to support patients in cardiogenic shock. Voudris et al.³⁰ reported the first European experience, and Kahn et al.³¹ reported the US experience with IABP to support high-risk PTCA. Both groups used depressed LV function or unprotected left main (UPLM) angioplasty as entry criteria.

HISTORY OF USE OF INTRAORTIC BALLOON PUMP DURING HIGH-RISK PERCUTANEOUS CORONARY INTERVENTION

The Mid America Heart group led by Dr. Goeffrey Hartzler pioneered the use of balloon angioplasty in patients with multivessel CAD.³² Similarly, this group first reported on adjunctive use of IABP in high-risk cases. Kahn et al.³¹ reported on 28 patients with a mean EFs of 24%, three-vessel diseases in 93%, and left main coronary artery (LMCA) lesions in 255 patients who had balloon angioplasty performed with IABP support. They found that augmented diastolic pressure greater than 90 mm Hg occurred in all cases. During hospitalization, no deaths were reported. Soon after, Voudris et al.³⁰ reported the initial European experience with supported HRPPI. In a 1-year period, 27 of 1385 patients in Toulouse, France, had supported HRPPI.³⁰ EF less

than 40% was present in 24 of 27 cases. No deaths or MIs occurred during initial hospitalization. The impact of poor ventricular function on outcomes was brought into clear focus by the NHLBI report in 1993. Holmes et al.³³ reported on 244 of 1802 patients treated in the 1985 to 1986 NHLBI PTCA registry who had EFs of 45% or less.^{9,33} Angioplasty was less successful (76% vs 84% $P < .01$), and the 4-year survival rate was lower than in patients with normal LV function.

With the advent of coronary stent implantation, PCI of UPLM intervention began in the early 1990s. Briguori et al.³⁴ reported the Milan, Italy, experience with stent implantation in 219 consecutive patients. Of these patients, 69 had prophylactic IABP support, and 150 had conventional unsupported procedures. Severe hemodynamic instability occurred in 8% of the unsupported group and none of the IABP group. Major adverse events were higher in the unsupported group (9.5% vs 1.5% $P = .032$). Thus, both depressed LV function and UPLM stent therapy started to be considered “high-risk” PCI.

More registry data continued to be reported concerning the value of IABP support. Mishra et al.³⁵ summarized the Washington Heart Center experience with prophylactic versus rescue IABP support. During a period from January 2000 to December 2004, outcomes of 68 patients with prophylactic IABP support were compared with 46 patients with IABP support started as a rescue for hemodynamic compromise. At 6-month follow-up, the mortality rate was lower (8% vs 29%; $P < .01$) and major adverse cardiovascular events (MACEs) were lower (12% vs 32%; $P = .02$) for patients with elective IABP support. Although these single-center reports suggested a safety advantage for elective IABP support, Curtis et al.³⁶ found a more mixed picture in the National Cardiovascular Registry. They reported outcomes from January 2005 to December 2007 in 181,599 HRPPI procedures; 1170 had cardiogenic shock, 80% had ST-elevation acute MI, 2% underwent unprotected LMCA PCI, and 20% had EFs less than 30%. An IABP was used in 44% of patients with cardiogenic shock, 28% of patients with UPLM, and 14% of patients with EF less than 30%; overall IABP support was used in 10.5% of HRPPI cases and varied widely from hospital to hospital. The hospitals were divided into quartiles of IABP use (6.5%, 6.6%–9.2%, 9%–14%, >14%). No convincing evidence was found that IABP use improved outcomes. The wide variation in IABP use rates across US hospitals suggested enormous operator preference and a lack of strong evidence for the elective use of prophylactic balloon pump therapy.

The IABP is constructed of a polyethylene balloon that is mounted onto a catheter that can be delivered through a sheath or sheathless to provide hemodynamic support in patients undergoing HRPPI. Although it may be inserted in the femoral artery without fluoroscopic guidance in an emergent situation, fluoroscopy is preferable when available to help with positioning. Before insertion of the balloon pump, a one-way valve is attached to the over-the-wire lumen, and a large syringe may be used to apply negative pressure to downsize the balloon to facilitate passage through the sheath. Using the standard technique, a Cook needle is used to access the femoral artery. A small incision may be made with a scalpel in the subcutaneous tissue,

and a sheath may then be delivered over a 0.035-inch wire. After the sheath is inserted, most kits contain a 0.018-inch wire that is inserted through the sheath into the ascending aorta. The balloon is advanced over this wire and delivered 2 cm distal to the left subclavian artery. After the position is verified, the inflation–deflation of the balloon pump is normally timed with electrocardiography monitoring of the console. The balloon can be filled with up to 50 cc of helium, which allows rapid inflation and deflation to provide both augmentation in coronary perfusion and unloading of the left ventricle during systole. In addition to placement through the femoral artery, the balloon pump may also be inserted into the axillary artery for patients with severe peripheral arterial disease. In the future, balloon pump shafts are small enough for 6-Fr access, in which case it is conceivable that radial access for balloon pump support may be feasible, at least for short-term use. Most balloon pump consoles may provide augmentation to heart rates up to 150 beats/min and may operate on battery power for limited time periods (Maquet Quick Reference Guide IABP insertion/CS300 Operation, 2014 Maquet). When heart rates greater than 130 beats/min occur, a 2:1 ratio of pumping allows optimal balloon pump inflation–deflation. Daily radiographs should be obtained to assure that catheter migration does not occur. In addition, knee splints are useful to place on the leg with the balloon pump inserted to immobilize the leg and prevent catheter dislodgment. If incremental support is required, balloon pumps may be exchanged for larger sheath sizes.

To do this, a stiff 260-cm 0.018-inch guidewire is advanced through the lumen of the balloon pump shaft, and the balloon pump is withdrawn. Negative pressure should be maintained with a large-bore syringe while the balloon pump is removed. After the balloon pump is removed, firm pressure is maintained at the puncture site while a 6- or 7-Fr sheath dilator is advanced. The dilator remains in place, the 0.018-inch wire is removed, and a 0.035-inch guidewire can then be advanced for upsizing of the sheaths. If concern exists at the time of the initial balloon pump insertion, a regular 8-Fr sheath can be used, the balloon pump can simply be removed, and a 0.035-inch guidewire can be advanced. The balloon pump may be inserted into the femoral or axillary artery to provide hemodynamic support.

BALLOON-PUMP ASSISTED CORONARY INTERVENTION STUDY

The equipoise that existed around routine IABP support for HRPPI allowed UK investigators to conduct the BCIS.⁹ This prospective randomized trial tested the strategy of routine, elective balloon pump support versus a provisional or standby strategy. Between December 2005 and January 2009, 301 patients with severe LV dysfunction or high jeopardy scores were randomized to IABP support or conventional care. It is not known how many patients were treated outside of this study in these centers. Physicians had to be unsure of whether the support was necessary to randomize patients. The primary endpoint of major adverse

cardiac and cerebrovascular events (MACCEs)—death, acute MI, cerebrovascular event, or further revascularization—occurred in 23 of 151 of elective IABP patients versus 24 of 150 control patients ($P = \text{NS}$). The 6-month mortality rate was 4.6% versus 7.4% ($P = 0.32$) for IABP versus the control group. During the procedure, major complications were less frequent in the IABP group (1.3% vs 10.7%; $P < 0.001$). Rescue IABP for profound procedural hypotension occurred in 18 (12%) of the control patients. The authors concluded that no evidence existed for a safety advantage to routine IABP use, although a trend to a lower mortality rate at 6 months was encouraging.

The BCIS investigators followed up with all patients for 5 years.³⁷ The original trend toward improved survival rate was enhanced after 5-year follow-up (Figure 5.10). At a mean follow-up of 51 months, 42 of 301 patients in the IABP group had died versus 58 of 300 patients in the control group ($P = .039$); thus, a 33% risk reduction had occurred. The mechanism for enhanced survival is unclear, yet similar trends are seen in the other revascularization trials, including SHOCK³⁸ and PROTECT II.⁸ In aggregate, these trials suggest a longer follow-up period is required to fully assess the impact of hemodynamic support in these high-risk patients.

With the recognition that more robust hemodynamic support might be required, Shawl et al.³⁹ and Vogel et al.⁵ reported experience with femoral–femoral CPS during elective angioplasty. Schreiber et al.⁴⁰ compared CPS with IABP in the William Beaumont Hospital experience. In this nonrandomized consecutive series, CPS use resulted in the greater angioplasty success (97% vs 87%; $P = .005$), but vascular complications requiring surgical repair were higher in the CPS groups, and the transfusions were higher in the CPS group (60% vs 27%; $P = .0001$). No formal randomized trials of CPS compared with unsupported care or other support devices have been conducted. IABP was well known and easy to use but might result in less complete revascularization and could not provide extreme

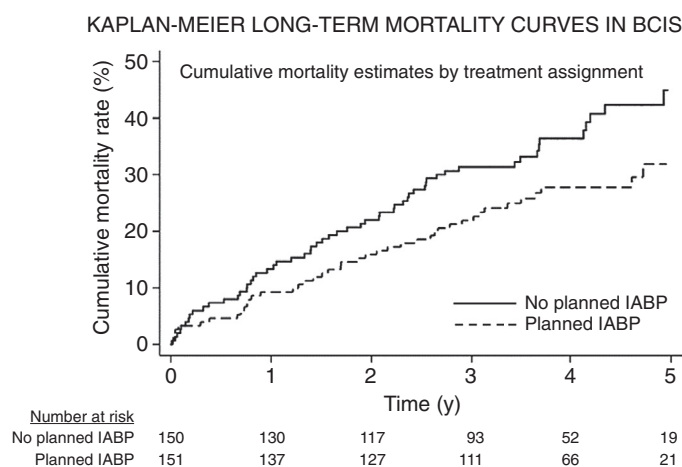


FIGURE 5.10 Balloon-Pump Assisted Coronary Intervention Study (BCIS) survival. Five-year survival rates for intraaortic balloon pump (IABP) control patients are depicted. A steady increase in mortality rate over time is seen for control-treated patients. (Reproduced with permission from Perera D, Stables R, Clayton T, et al. Long-term mortality data from the balloon pump-assisted coronary intervention study (BCIS-1): a randomized, controlled trial of elective balloon counterpulsation during high-risk percutaneous coronary intervention. *Circulation*. 2013;127(2):207-212.)

support when intrinsic myocardial function was absent. Although CPS provided excellent systemic support, the large arterial cannulas and blood interface with the membrane oxygenator caused excessive bleeding and vascular complications. More worrisome, Stack et al.⁴¹ showed that initiation of CPS caused frank myocardial ischemia as demonstrated by myocardial lactate production in this high-risk PTCA population.¹ In addition, Pavlides et al.⁴² demonstrated that regional wall motion of myocardial segments supplied by vessels with greater than 50% stenosis worsened with initiation of CPS. For these reasons, alternative hemodynamic support methods that provided both systemic and myocardial support were sought.

HISTORY OF TANDEMHEART DEVELOPMENT

Because elevated left-sided filling pressures are a hallmark of patients with severe LV dysfunction, support devices that unload the LV during PCI are important to decrease wall tension and MVO_2 . One of these devices is the TandemHeart percutaneous ventricular assist device (Figure 5.11). The TandemHeart is a centrifugal continuous flow pump.⁴³ A 21-Fr venous inflow cannula is placed through the femoral vein up and across the interatrial septum via a transeptal puncture into the left atrium. A second 14- to 19-Fr cannula is then placed into the femoral artery. Oxygenated blood is removed from the left atrium and delivered to the

descending aorta, effectively unloading the left ventricle in both systole and diastole. At a maximum speed of 7500 rotations per minute (RPM), the TandemHeart can deliver up to 4 L of flow per minute.

The experience with TandemHeart in HRPPI is restricted primarily to single-center registry studies. Two small studies with fewer than 10 patients each demonstrated 100% procedural success with TandemHeart-assisted PCI in high-risk patients with severe LV dysfunction⁴⁴ and in UPLM disease in patients who were deemed unsuitable for CABG.⁴⁵ Schwartz et al.⁴⁶ showed, in a cohort of 32 TandemHeart patients, a 100% success rate with device initiation and a 97% angiographic success rate. One patient had an embolic stroke, which was presumed to be from aortic atheroma, and there were two cases of limb ischemia, which resolved with device removal or repositioning. Finally, Kovacic et al.⁴⁷ compared the use of TandemHeart versus Impella 2.5 in a group of patients who were deemed at high risk. PCI success rate was 99% in both groups. The 30-day rate of death; death or MI; and death, MI, or target lesion revascularization was similar between the two groups. There was a single case of left atrial perforation with initiation of the TandemHeart.⁴⁷ These studies demonstrate the high technical success rate for revascularization in patients who are supported with the TandemHeart during HRPPI. Because of a lack of randomized trial data and need for transeptal puncture, this device is not widely used today.

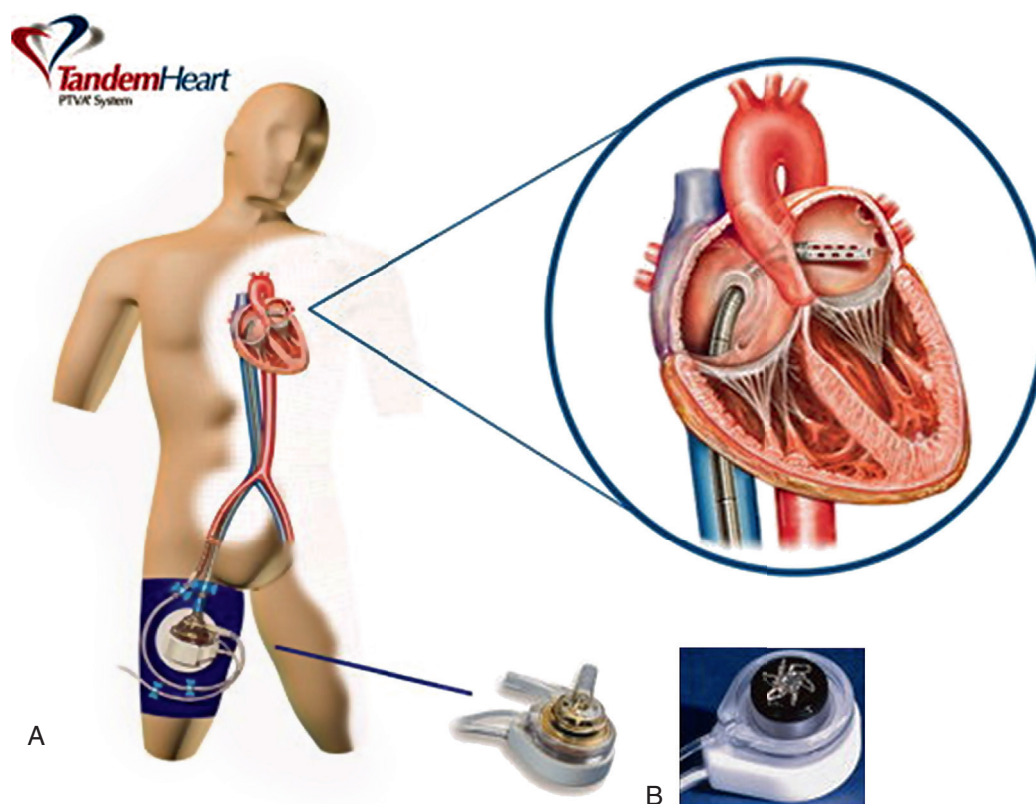


FIGURE 5.11 Cardiac assist device (A and B). TandemHeart placement occurs through the femoral artery and vein. A large venous catheter is placed through the intraatrial septum to pump oxygenated blood from the left atrium, and this blood is sent through the centrifugal pump back into the femoral artery. (Reproduced with permission from Vranckx P, Otten A, Schultz C, et al. Assisted circulation using the TandemHeart, percutaneous transeptal left ventricular assist device, during percutaneous aortic valve implantation: the Rotterdam experience. *EuroIntervention*. 2009;5(4):465-469.)

TRANSVALVULAR AXIAL FLOW PUMPS

The first transvalvular axial pump was developed by Wampler's group.⁴⁸ The Hemopump was an intraarterial LVAD that was initially tested in a surgical environment. The device was a 7-mm transvalvular axial flow blood pump. It was powered by an external console with power delivered to the pump by a flexible drive cable. Frazier et al.⁴⁹ described its use in 12 patients, 8 of whom had postcardiotomy shock, 2 with acute allograft reaction, and 1 with MI shock. Support ranged from 26 to 139 hours, and 10 of 12 patients were successfully weaned off support. The large catheter size (21 Fr) mandated surgical access and repair.

For this device to be applicable to the catheterization laboratory setting, a smaller shaft size was required. For this reason, a 14-Fr catheter was developed. Panos et al.⁵⁰ described the use of this device in 13 patients who were treated in Geneva between 1993 and 1996. The device had a 14-Fr outer diameter and could provide flow rates of 1.5 to 2.2 L/min (Figure 5.12). A modest increase in cardiac index (2.0 ± 0.3 to 2.2 ± 0.5 ; $P = .04$) and modest decrease in PCWP (17 ± 8 to 14 ± 8 ; $P = .004$) occurred. No in-hospital deaths occurred. Dubois-Rande et al.⁵¹ demonstrated that PCWP decreased, but no changes in coronary blood flow occurred when 13 patients undergoing HRPDI were treated. Although this initial experience was encouraging, during subsequent testing, an unacceptably high

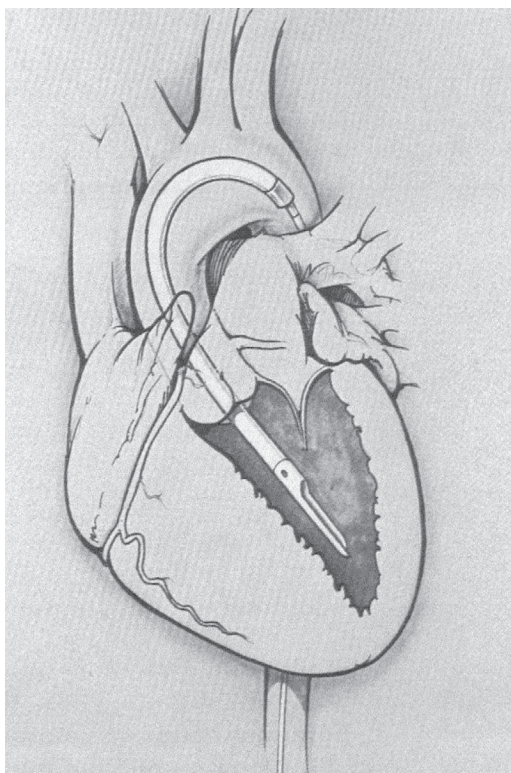


FIGURE 5.12 Transfemoral Hemopump placement. The Hemopump was placed from the femoral or iliac arteries. A long flexible drive shaft was connected to the catheter tip. The drive shaft was attached to an external motor. The length and high speeds required made frequent drive shaft fracture a major obstacle to chronic support. (Reused with permission from Frazier OH, Wampler RK, Duncan JM, et al. First human use of the Hemopump, a catheter-mounted ventricular assist device. *Ann Thorac Surg.* 1990;49(2):299-304.)

rate of cable fractures was reported, and the device was abandoned. At least the concept of a transvalvular axial flow device was established. Two other cable driven axial flow pumps, one by Abbott Vascular and one by CSI, are under development. No clinical data are yet available.

HISTORY OF IMPELLA DEVELOPMENT

After the Hemopump demonstrated proof of the concept of a transvalvular axial flow hemodynamic support, Cardiosystems GmbH developed a series of LVADs and right ventricular assist devices (RVADs). The LV system was a microaxial flow pump 6.4 mm in diameter. The pump was placed at the tip of the catheter, and this was designed to be inserted through a graft placed on the aorta and advanced retrograde across the aortic valve. Initially, rotor speeds of up to 32,000 RPM could supply up to 5.2 L of flow. The electrical power was provided through the shaft of the catheter, and the Impella housing was flushed continuously with hyperosmolar, heparinized solution to prevent clotting in the pump. An RVAD was also designed. It, too, was meant to be inserted during cardiac surgery.

These implants were developed as adjuncts to beating heart surgery.⁵² At that time, beating heart surgery was gaining traction as a potentially safer way of performing CABG without use of the pump oxygenator. Surgeons had difficulty performing anastomosis in the back and inferior border of the left ventricle during off-pump surgery. When the heart was lifted to explore these areas, profound hypotension occurred. The Impella catheters were designed to be placed by puncture of the aorta for the LV support and by puncture or grafting onto the pulmonary artery for right ventricular support (Figure 5.13). Meyns et al.⁵³ published a small, randomized trial of support with Impella versus normothermic cardiac bypass. Although support of the heart during off-pump surgery was the initial reason for development, other uses soon became evident. From

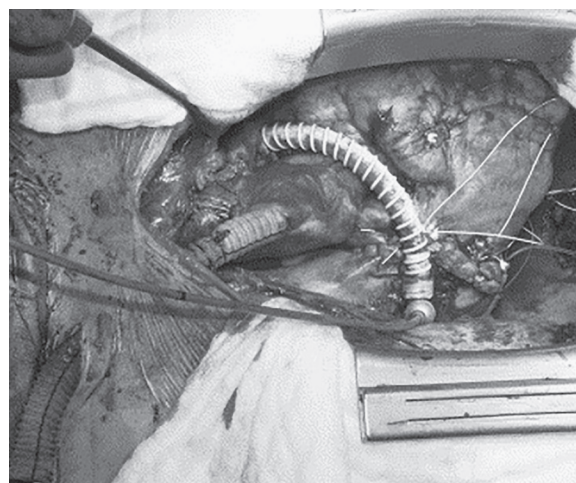


FIGURE 5.13 Right ventricular support. Open thoracotomy. The patient's head is to the left. An aortic graft allows access to the aortic valve for the left heart support, and a graft is sewn from the right atrium to the pulmonary artery for the right heart support. (Reused with permission from Jurmann MJ, Siniawski H, Erb M, et al. Initial experience with miniature axial flow ventricular assist devices for postcardiotomy heart failure. *Ann Thorac Surg.* 2004;77(5):1642-1647.)

January 2001 to September 2002, 16 patients in cardiogenic shock refractory to inotropic support were treated by Meyns et al.⁵³ Excellent hemodynamic support was achieved with increased cardiac output (4.1 to 5.5 L/min; $P = .01$), mean PCWP decreased (29 ± 10 to 18 ± 7 ; $P = .04$), and MAP increased (74.9 ± 13 to 80.6 ± 17 mm Hg; $P = .003$). The increased cardiac flow caused a reduction in serum lactate levels at 6 hours of support. Despite these beneficial hemodynamic and biochemical findings, only a 37% survival rate occurred. A common theme with ECMO and the TandemHeart began to emerge. All three devices provided excellent short-term support that were lifesaving in the short term. Without a more definitive end strategy (LVAD or transplant), fewer than 50% of these extreme shock patients survive.

After this initial experience, a second-generation Impella microaxial pump was developed. The Impella Recover LP 2.5 device had a decreased shaft size to allow passage of the device through a 13-Fr sheath. Dens et al.⁵⁴ first reported

outcomes in 13 patients in the shock and 27 patients undergoing HRPIC. The initial device caused hemolysis in 9 patients, and the device malfunctioned in 3. The device was modified, and no further failures occurred. The device improved cardiac output (4.4 to 4.81 L/min; $P = .018$) and decreased wedge pressure (22 ± 7.5 to 16 ± 6 mm Hg; $P = .0008$) after 6 hours. Although the Impella devices were originally designed as surgically implanted micro-ventricular assist devices (VAD's), downsizing of the catheter and shaft as well as placement of the pigtail on the tip allowed the potential for transfemoral access. The initial use of the Impella Recover 2.5 device in HRPIC was described by Valgimigli et al.⁵⁵ A 56-year-old patient with four previous MIs and chronic EF of 27% was admitted with unstable angina. There was a severe, ulcerated culprit lesion of a large dominant left circumflex vessel. Before PCI was performed, hemodynamic changes and pressure-volume loops were obtained (Figure 5.14). During high flows (50,000 RPM), LV volumes were reduced, systolic pressure

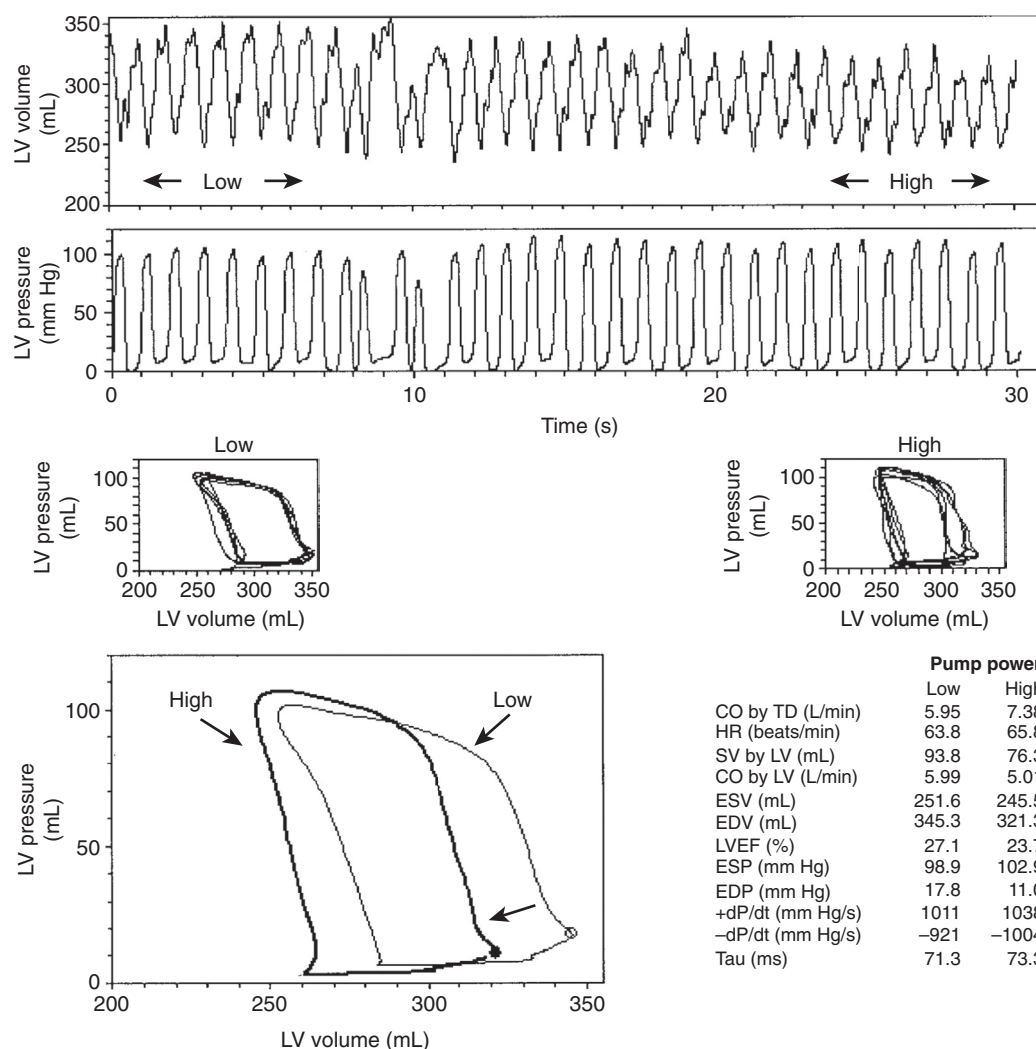


FIGURE 5.14 Pressure-volume loops (P-V) during Impella support. During high flows, left ventricular (LV) volumes diminish (*upper panel*), and LV pressures remain constant (*second row*). The average of P-V loops are present in the *lower row*. During high flow, LV end-diastolic pressures are decreased, and systolic pressures are maintained or augmented. CO, Cardiac output; dP, delta pressure; dt, delta time; EDP, end diastolic pressure; EDV, end diastolic volume; ESP, end systolic pressure; ESV, end systolic volume; HR, heart rate; LVEF, left ventricular ejection fraction; SV, stroke volume. (Reproduced with permission from Valgimigli M, Steendijk P, Sianos G, et al. Left ventricular unloading and concomitant total cardiac output increase by the use of percutaneous Impella Recover LP 2.5 assist device during high-risk coronary intervention. *Cathet Cardiovasc Interv*. 2005;65(2):263-267.)

was elevated, and LV filling pressures were reduced. These changes would all be expected to decrease MVO_2 while maintaining or increasing coronary blood flow. Rummelink et al.⁵⁶ confirmed the beneficial effects of Impella support on coronary hemodynamics. This group studied 11 patients undergoing HRPPI and assessed coronary pressures and flow velocity in nondiseased coronaries or after stent implantation of a last patent vessel. They found that coronary pressures were elevated by Impella support. Coronary flow velocity was increased, and coronary microvascular resistance was reduced with increasing levels of support. Unfortunately, no data were collected on pressure and flow distal to stenotic segments. At the same time, Rummelink et al.⁵⁷ further elaborated the hemodynamic benefit of the Impella catheter. This group further analyzed wall stress and LV volume. During high-level support, systolic pressure was maintained, LVEDP was dramatically reduced, and wall stress was reduced (Figure 5.15). The beneficial effects on coronary flow and microvascular resistance along with decreases in LV wall stress appeared to be ideal for hemodynamic support during HRPPI.

CLINICAL TRIALS OF IMPELLA IN HIGH-RISK PERCUTANEOUS CORONARY INTERVENTION

Henriques et al.⁵⁸ reported a series of 19 HRPPI patients with the Impella LP 2.5-supported system. This report

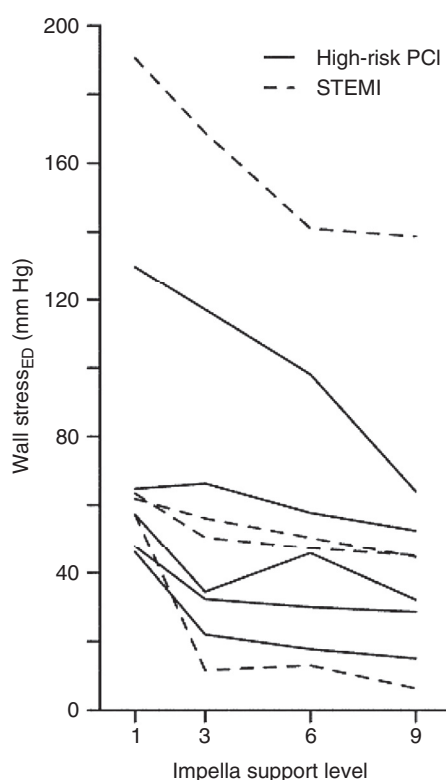


FIGURE 5.15 Pressure–volume loops during Impella support. Increasing support decreases left ventricular wall stress in both high-risk percutaneous coronary intervention as well as patients with ST-segment elevation myocardial infarction (STEMI) being treated with percutaneous coronary intervention (PCI) therapy. (Reproduced with permission from Rummelink IM, Sjaun KD, Henriques JP, et al. Effects of left ventricular unloading by Impella Recover LP2.5 on coronary hemodynamics. *Cathet Cardiovasc Interv*. 2007;70(4):532-537.)

summarized the Academic Medical Center Experience from October 2004 to August 2005. In this study, echocardiograms were reported, and no increase in aortic regurgitation was found. They first described the preclosure techniques of placing double Perclose (Abbott Laboratory) devices for vascular closure in 15 of 19 patients (Figure 5.16). This series included all patients with EFs of 40% or less and 12 of 19 patients with EFs of 25% or less. Ten patients had PCI of the left main or last patent vessel. Successful Impella placement occurred in all patients. One of the patients was excluded because of the presence of intraventricular thrombus. The Impella was successfully removed in the elective cases, and no vascular complications occurred. Thus, elective HRPPI appeared feasible but needed to be prospectively tested.

The device received a Conformite Europeenne mark in 2004. Sjaun et al.⁵⁹ published the initial European (Europella) registry. This report summarized the clinical outcome in 144 consecutive patients who underwent HRPPI. PCI was considered high risk because of left main disease, last patent coronary vessel, or multivessel disease with low EF. A 30-day mortality rate of 5.5% occurred. In addition, 5.5% of the patients required blood transfusions, and one stroke was reported. These results were at least comparable to previous registry reports of HRPPI.

In July 2006, the US safety and feasibility trial was initiated. Dixon et al.⁶⁰ reported outcomes on 20 patients undergoing HRPPI. The study was performed to provide US operators with experience and to determine MACE endpoints for sample size calculation for the pivotal randomized trial. To be included, patients were required to have EFs of 35% or less and were about to undergo PCI of LMCA or last patent vessel. Patients with MI within the previous 24 hours, with documented LV thrombus, with presence of mechanical aortic prosthetic valve, or with aortic stenosis with a valve area of 1.5 cm² or less were excluded. Of the 20 patients enrolled, 14 underwent the LMCA PCI, and 6 had the last patent vessel treated. The mean duration of support was 1.7 ± 0.6 hours. Mean pump flow was 2.2 L/min. All devices were successfully removed, and no reports of device malfunction occurred. At 30 days, an adverse safety endpoint had occurred in 20% of patients. Echocardiograms performed at baseline and 30 days found no damage to the aortic valve and an improved EF (25 ± 10 to 33 ± 10 ; $P < .001$). Two patients had laboratory evidence of mild hemolysis. There were two deaths at 12 and 14 days after PCI. During the procedure, all patients had freedom from hemodynamic compromise, although one patient had moderate aortic regurgitation during Impella support, which resolved with a device explant. The results of this trial were encouraging and allowed planning for the definitive randomized trial of Impella during HRPPI.

PROTECT II

After completion of the PROTECT I trial, Abiomed petitioned the Food and Drug Administration (FDA) to conduct a pivotal randomized trial.⁸ At the same time, it applied for 510(k) clearance based on data obtained in

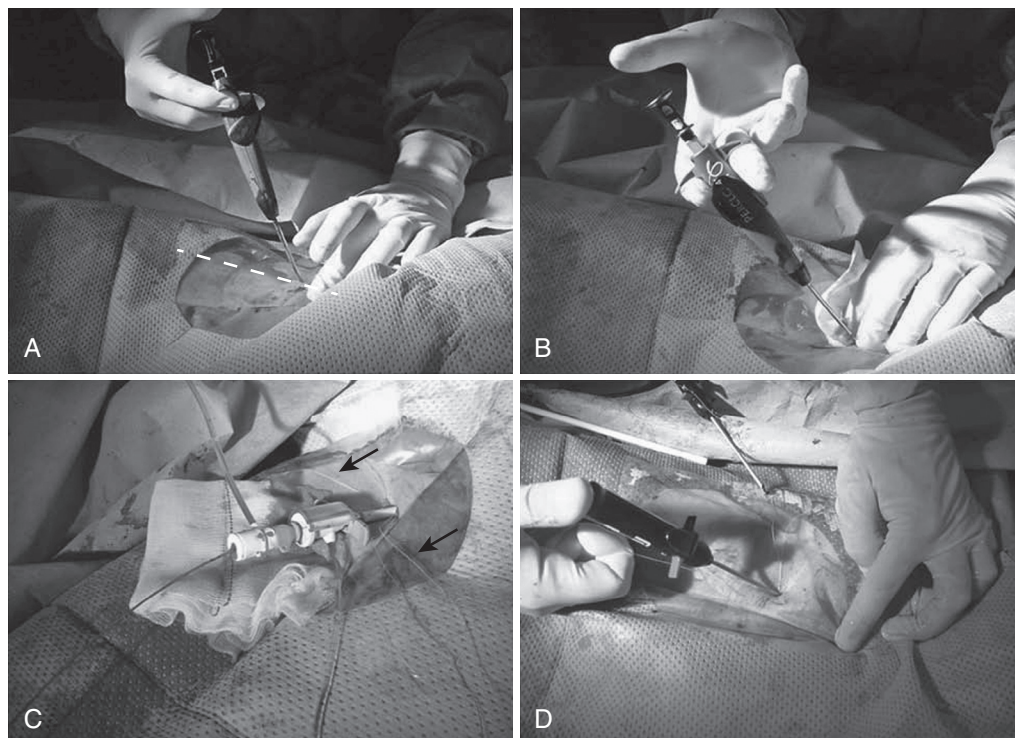


FIGURE 5.16 Perclose technique for large vessel hemostasis. Before placing Perclose (Abbott Labs) sutures, femoral angiography is performed to assure access is in the common femoral artery. Two Perclose devices are placed at 90-degree angles (**A** and **B**). The large sheath is then inserted (**C**). At the end of the procedure, both sutures are tied sequentially (**D**). If bleeding persists, manual pressure can be applied. This technique should not be used when sheaths remain in place for chronic support. (Reproduced with permission from Dangas GD, Kini AS, Sharma SK, et al. Impact of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump on prognostically important clinical outcomes in patients undergoing high-risk percutaneous coronary intervention (from the PROTECT II randomized trial). *Am J Cardiol.* 2014;113(2):222-228.)

Europe and the PROTECT I trial. In negotiations with the FDA and using the PROTECT I data, a 30% major adverse event (MAE) rate was assumed for control-treated patients, and a reduction to 20% MAE by Impella was hypothesized. A sample size of 654 patients was required to achieve an 80% power and two-sided alpha error of 5%. A 30-day endpoint was a standard FDA-required period. In addition, because these high-risk patients may not stabilize at 30 days, a 90-day endpoint was prospectively mandated. Both intentions to treat and per protocol analysis were reported to test the treatment and device strategies.

Prospective subgroup analysis was predetermined. First, there was a concern that because the device was new, a learning curve might exist. Because the company could not afford the cost of supporting a learning curve at each site, a learning curve analysis whereby each center's first patient was excluded was performed. Second, there was a concern that the use of rotational atherectomy might cause excessive cardiac enzyme elevations; for this reason, an analysis of patients treated with and without rotational atherectomy was conducted. Finally, society of thoracic surgeons (STS) level and treatment of LMCA versus three-vessel disease was also evaluated prospectively.

The PROTECT II study commenced enrollment in November 2007. In July 2008, FDA 510(k) clearance for the device occurred. This commercial approval led to a slow-down in recruitment because some high-volume centers chose to stop enrollment in the trial and only treat HRPDI patients with commercially available Impella support. An independent Data Safety Monitoring Board (DSMB) was

charged with a review of safety and provided an unblinded analysis at 25% and 50% recruitment levels. At the 50% enrollment level, the DSMB recommended cessation of the enrollment because 30-day efficacy endpoints were similar, and the board concluded that a significant difference would be unlikely. By the time this recommendation was received, 70% of the enrollment target had been achieved. The entire trial experience was analyzed and reported. In retrospect, it is unfortunate that the DSMB did not take the 90-day endpoint into the efficacy analysis and could not have known the strong influence of a learning curve that existed for the device (Figure 5.17).

In total, 448 patients were randomized and analyzed according to intention-to-treat (ITT) principles; 427 patients were examined to meet entry criteria and were analyzed by protocol (PP) principles. Thus, both the strategy (ITT) and the device (PP) were tested. During the PCI procedure, the Impella provides unequivocally better hemodynamic support. There were fewer hypotensive events (0.45 ± 1.37 vs 0.96 ± 2.05 events per patient; $P = .001$) with Impella versus IABP support. Cardiac power was better preserved with less of a decrease in cardiac power (-0.04 ± 0.24 vs -0.14 ± 0.27 watts; $P = .001$) for Impella support. In other words, fewer hypotensive events and better cardiac power protection occurred with Impella therapy. The primary endpoints are demonstrated in Figure 5.18. A review of the Kaplan-Meier event-free survival curves demonstrates that slight differences existed between the two groups out of 30 days. At 90 days, however, there was a difference in outcomes, with Impella-treated patients having

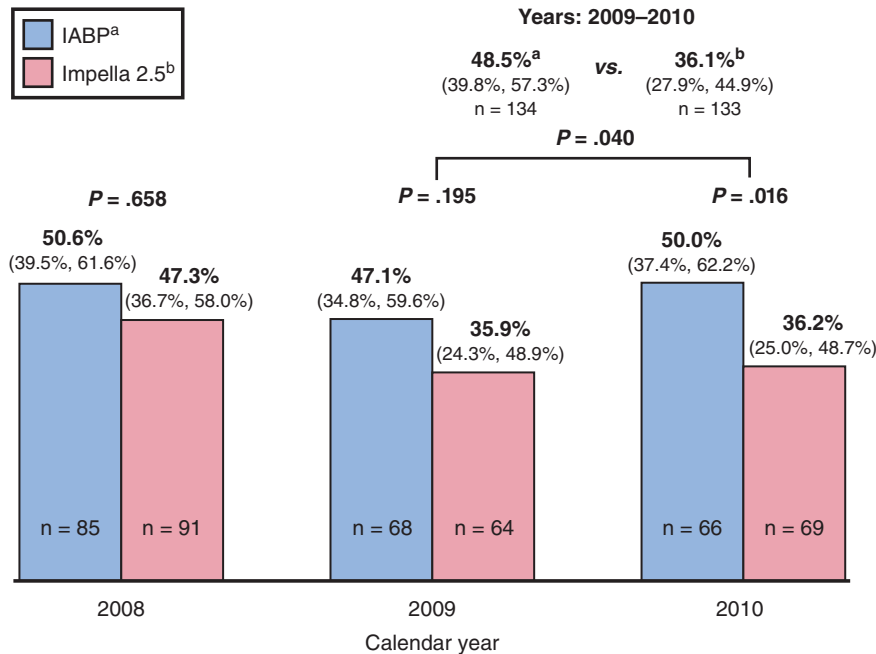


FIGURE 5.17 Learning curve for Impella therapy in the PROTECT II trial. Major adverse outcomes are presented based for the year patients were treated. Because intraaortic balloon pump (IABP) is a well-established therapy, event rates were similar in all 3 years; conversely, event rates significantly dropped in 2009 and 2010 for Impella-treated patients. (Reproduced with permission from Henriques JP, Rummelink M, Baan J Jr, et al. Safety and feasibility of elective high-risk percutaneous coronary intervention procedures with left ventricular support of the Impella Recover LP 2.5. *Am J Cardiol.* 2006;97(7):990-992.)

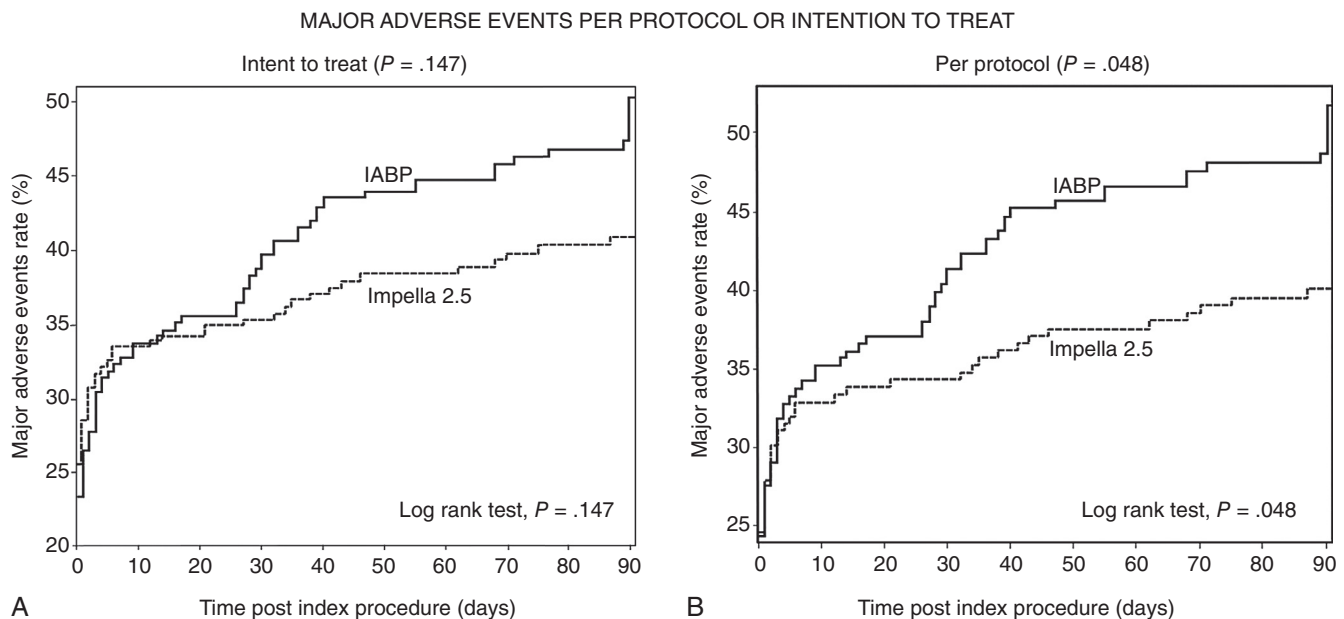


FIGURE 5.18 PROTECT II overall results (A and B). Event curves demonstrate that after 30 days, many overt clinical events occurred, particularly in intraaortic balloon pump (IABP)-treated patients. (Reproduced with permission from O'Neill WW, Kleiman NS, Moses J, et al. A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: the PROTECT II study. *Circulation.* 2012;126(14):1717-1727.)

a higher rate of event-free survival. The events after the 30-day endpoint occurred in an outpatient population. These events were overt and included death, reinfarction, stroke, repeat hospitalization, and repeat coronary intervention. In addition to the overall results, two prospectively designed subgroup analyses have been reported.

First, Cohen et al.⁶¹ demonstrated that Impella-assigned patients had rotational atherectomy used at a higher

frequency (8 vs 14%; $P = .08$). In addition, Impella-treated patients had more aggressive atherectomy with a longer duration of passes and more frequent passes for left main obstructions. This resulted in a higher rate of cardiac enzyme elevation, which resulted in a higher rate of periprocedural MI. For 88% of patients treated without atherectomy, a major benefit existed at both 30- and 90-day endpoints (Figure 5.19).

IMPACT OF ROTATIONAL ATHERECTOMY ON OUTCOMES IN PROTECT II

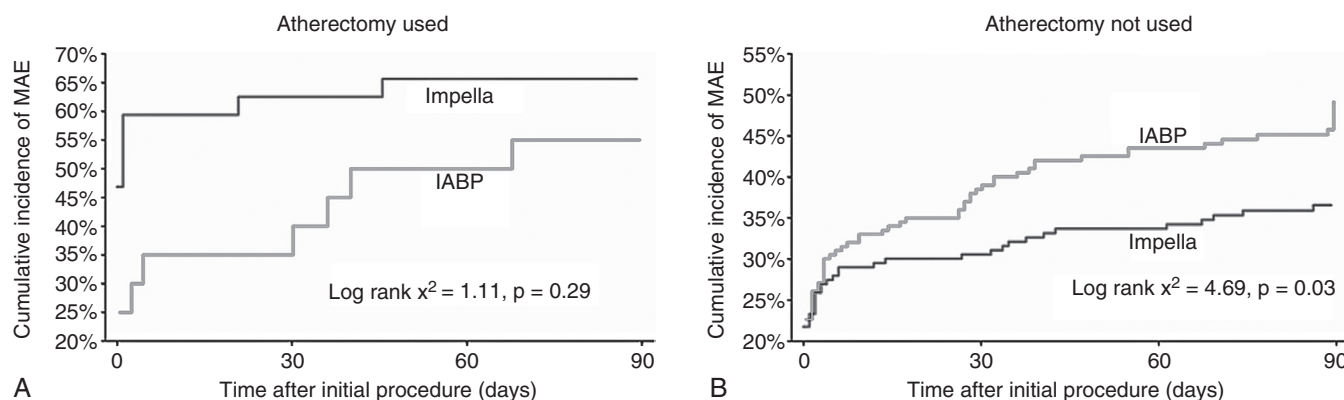


FIGURE 5.19 Event curves for patients treated with atherectomy are depicted in **A** and patients with stent therapy alone in **B**. For 885 patients treated without atherectomy, a significant reduction in major adverse events occurred at both 30 and 90 days. (Reproduced with permission from Cohen MG, Ghatak A, Kleiman NS, et al. Optimizing rotational atherectomy in high-risk percutaneous coronary interventions: insights from the PROTECT II study. *Cathet Cardiovasc Interv*. 2014;83(7):1057-1064.)

A second substudy publication describes the learning curves that existed. Henriques et al.⁶² analyzed outcomes for the entire population, and the first patient who enrolled was removed from the trial. Because many of the centers used Impella for the first time in this trial, the learning curve was embedded in the overall results. After operators became proficient, a significant improvement in outcome occurred for Impella-treated patients. In addition to these two prospective subgroups' publications, two other important post hoc analyses have been published. Dangas et al.⁶³ reported on the major impact that the definition of periprocedural MI has on the outcomes in PROTECT II. Before the PROTECT II trial was conducted, the FDA recommended a historic definition of periprocedural MI, which was an elevation of cardiac enzymes three times the upper limit of normal for each institution. This definition has been called into question since Stone et al.⁶⁴ published a meta-analysis of 8000 patients treated in modern device trials. These authors demonstrated that prognostically important cardiac enzyme elevation was 8 times the upper limit. When an $8\times$ level was analyzed by Dangas in the PROTECT II population, a significant improvement in event-free survival occurred for Impella-treated patients both at 30- and 90-day time points (Figure 5.20). Overall, no difference in the incidence of negligible MI or large prognostically significant MI occurred. A doubling incidence of small MI (>3 to $<8\times$ elevation of cardiac enzymes) (9 of 124 vs 18 of 225; $P = .078$) occurred for Impella-treated patients. A multivariable analysis demonstrated that Impella use resulted in a 25% risk reduction (odds ratio, 0.76; confidence interval, 0.61–0.96; $P = .02$) at 90 days.

Kovacic et al.⁶⁵ presented an initial analysis of outcomes for patients based on the number of lesions treated. When one vessel is intervened, little difference occurs between Impella and IABP. Conversely, when two or more vessels are treated, a marked reduction in cardiac power occurs in the IABP-treated patients compared with the Impella-treated ones. The 90-day outcomes were significantly improved for Impella-treated patients when two or more vessels were treated.

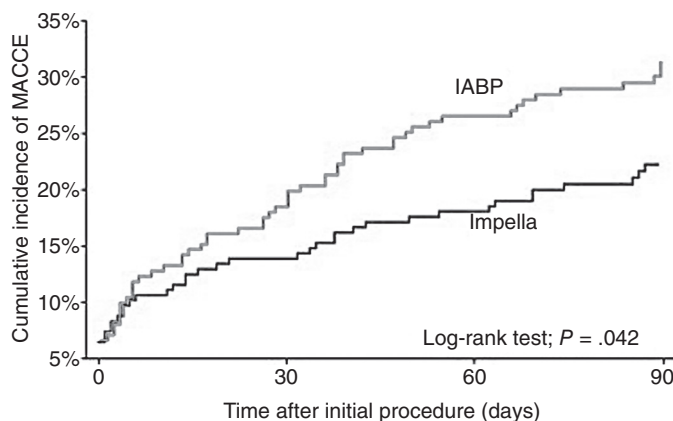


FIGURE 5.20 Major adverse cardiac and cerebrovascular events (MACCEs) with a greater than eight times increase in creatine kinase-MB were compared for Impella and balloon pump patients. A significantly lower risk for MACCEs occurred over the 90-day follow-up for the Impella group. IABP, Intraaortic balloon pump. (Reproduced with permission from Dangas GD, Kini AS, Sharma SK, et al. Impact of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump on prognostically important clinical outcomes in patients undergoing high-risk percutaneous coronary intervention (from the PROTECT II randomized trial). *Am J Cardiol*. 2014;113(2):222-228.)

When the overall trial results and subgroup reports are considered together, a clear picture for the value of Impella in HRPPI emerges. First, when a new device is tested, a learning curve exists, and procedural outcomes are expected to improve over time. In the PROTECT II study, outcomes were far better after the learning curve was overcome. Next and most important, trials of HRPPI must report long-term outcomes in analysis of efficacy. The traditional 30-day surgical endpoint is insufficient. Both the Shock⁶⁶ and BCIS³⁷ trials were neutral at 30 days and showed superiority for balloon pump therapy at 1 or 5 years. Outpatient events continue to occur over the first 90 days, so it is insufficient to use in-hospital or 30-day outcomes to assess efficiency of a support strategy. Furthermore, the definition of periprocedural MI that uses prognostically relevant ($>8\times$) enzyme elevations shows that Impella support

decreases adverse events compared with IABP. The patients most likely to benefit are treated with stent implantation unassisted by rotational atherectomy. When atherectomy is used, fewer, shorter passes are recommended. Finally, the advantage of Impella over IABP is most pronounced when multiple vessels are intervened. In these patients, Impella provides far superior hemodynamic support and results in improved event-free survival at 90 days.

In addition to hemodynamic support, use of Impella may provide protection against acute kidney injury (AKI). Flaherty et al.⁶⁷ analyzed two independent data sets on this issue. Their first data set reported a single-center experience in which 115 consecutive patients undergoing elective, urgent, or emergent HRPPI were compared with a sex, age, and baseline glomerular filtration rate control group. They found a reduction of AKI at 72 hours from 27.8% to 5.27% ($P < .001$). To expand on these observations, they explored the catheter-based ventricular assist devices (cVAD) registry database.⁶⁸ The Mehran risk score⁶⁹ was used to calculate risk of AKI in 223 patients undergoing nonemergent HRPPI at the 43 participating centers overall 4.5% of the supported HRPPI patients developed AKI at 48 hours versus a predicted rate of 21.9% ($P < .0001$). These observations will be formally tested in the PROTECT IV randomized trial or a major secondary efficacy endpoint.

OPTIMAL USE OF IMPELLA FOR HEMODYNAMIC SUPPORT

The PROTECT II trial was conducted at the dawn of Impella use in the United States. Over the past 10 years, as widespread use of ultrasound-assisted micropuncture of the common femoral artery was developed, suture-mediated closure of the vessel with preclose devices (Abbott Vascular) became dominant. In addition, best practices were adopted to attempt more complete revascularization so that long-term outcomes could be improved. Also, the Impella CP catheter was introduced. This device provides up to 4 L/min of forward flow.

To determine whether refinement in vascular access and closure and an attempt at more complete revascularization would alter outcomes, data from the ongoing cVAD registry were compared with the historic Impella-treated patients in the PROTECT II study.⁷⁰

From March 2017 to March 2020, 43 highly experienced centers treated 1143 patients with elective or urgent supported PCI. Of these patients, 504 met eligibility criteria for PROTECT II. There were labeled PROTECT III. The PROTECT III patients were older (69.3 ± 11 vs 67.5 ± 11 ; $P = .05$), had fewer previous CABG procedures (13.7% vs 39.4%; $P < .001$), and had fewer previous MI (41% vs 69%; $P < .001$). Importantly, EF for PROTECT III patients was equally depressed (LVEF $22.6 \pm 7\%$ vs $23.4 \pm 6\%$; $P = .148$). Figure 5.21 summarizes anatomic and procedural

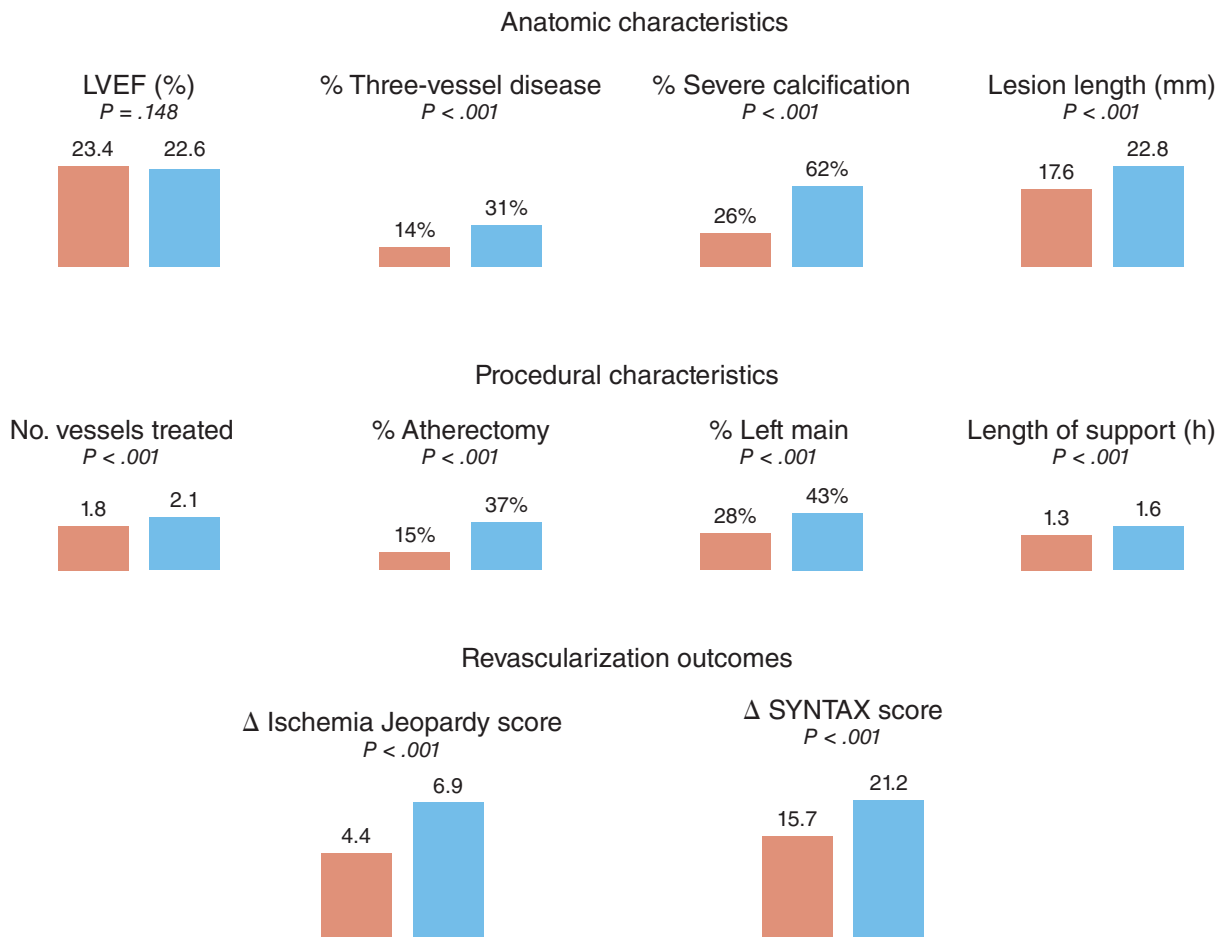


FIGURE 5.21 Summary of the anatomic, procedural characteristics, and revascularization extent. It can be seen that the longer, more heavily calcified lesions were treated in PROTECT III. Despite this, more extensive revascularization is measured by lower residual ischemia and SYNTAX scores occurred.

characteristics and revascularization extent. It can be seen that patients with longer, more heavily calcified lesions were treated in PROTECT III. Despite this, more extensive revascularization is measured by lower residual ischemia and SYNTAX scores occurred.

These improved revascularization results were accompanied by lower bleeding academic research consortium (BARC) 3 to 5 bleeding risks (9.4% vs 1.2%; $P < .001$), less severe hypotension (10.4% vs 1.9%; $P = 0.004$), and less cardiopulmonary resuscitation or ventricular tachycardia risk (6.6% vs 0.2%; $P = .03$). The new vascular access and closure and have more powerful Impella platform thus has made procedures more thorough and safer.

Not only are hospitalization outcomes improved, but 90-day event free survival is also significantly improved. At 90 days, MACCEs were reduced from 21.9% to 15.1% ($P = .037$). After propensity matching, Kaplan-Meier analysis showed reduction in 90-day MACCEs from 16.9% to 10.4% ($P = .048$). When the entire PROTECT II population is compared with the PROTECT III population (Figure 5.22), a dramatic reduction in 90-day MACCE event rate has occurred.

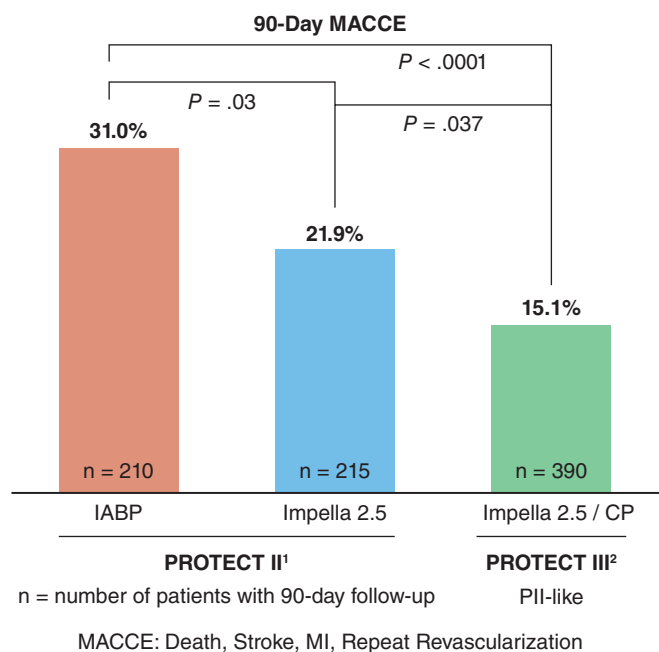
CASE EXAMPLE

The use of Impella 2.5 support was demonstrated in a patient treated at the Henry Ford Cath Lab in August 2013. This was an 85-year-old Jehovah's Witness who was

catheterized at a referral institution 2 weeks before admission. She presented with non-ST-segment elevation myocardial infarction and underwent catheterization. She was found to have impaired LV function, total occlusion of the proximal right coronary artery, and a complex calcified bifurcation left main lesion with calcified lesions of the proximal LAD and obtuse marginal as well. After catheterization, she developed radiocontrast nephropathy and was deemed not a surgical candidate. The patient was referred for HRP. Over a 2-week period, her renal function returned to baseline.

Initially, an abdominal angiogram (Video 5.1) was performed, and both iliac arteries were suitable for access. The Impella 2.5 device was delivered through a sheath in the left femoral artery, and a preclose technique was used. After the Impella was in place, p-8 flow rates were obtained, and an output of 2.4 L/min was attained (Video 5.2). A complex intervention was initiated, with atherectomy performed in the LMCA (Video 5.3 to 5.5) as well as LAD and OM branches (Figure 5.23). Subsequently, simultaneous balloon inflations were performed in the LAD and circumflex vessel. During this time, no coronary blood flow was possible (Video 5.6). During balloon inflation, pulsatile flow ceased, yet pulmonary artery pressures were maintained, and MAP remained at 100 mm Hg. Immediately after balloon deflation, systemic pressure returned to

PROTECT III shows improved outcomes in contemporary practices



1. Dangas G, et al. Am J Cardiol. 2014;113(2):222-228
2. O'Neill W, et al. PROTECT III Study. Publication Pending

FIGURE 5.22 At 90 days, major adverse cardiac and cerebrovascular events (MACCEs) were reduced from 21.9% to 15.1% ($P = .037$). After propensity matching, Kaplan-Meier analysis showed a reduction in 90-day MACCE from 16.9% to 10.4% ($P = .048$). When the entire PROTECT II population is compared with PROTECT III, a dramatic reduction in 90-day MACCE event rate is seen to have occurred.

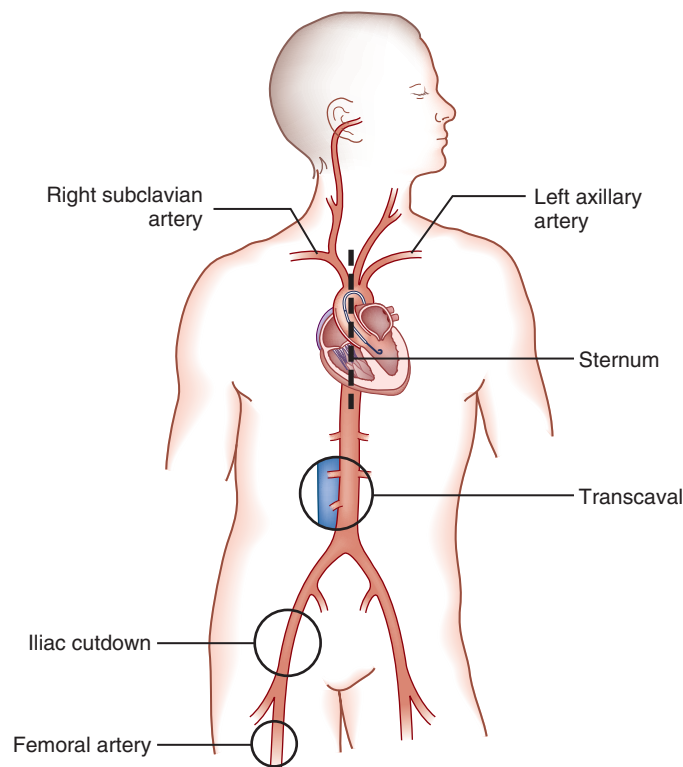


FIGURE 5.23 Access for large-bore hemodynamic support devices. Arterial access is a major challenge for the safety of large-bore left ventricular support devices. Typically, percutaneous puncture of the common femoral artery is the first choice. When the femoral cannulation is not possible, surgical cutdown of the iliac artery through a lateral peritoneal approach and cutdown of either the right or left axillary artery can occur. For longer support, a chimney graft can be inserted into the right subclavian artery. A direct puncture of the aorta with a ministernotomy is feasible in the surgical population. (Courtesy of Dr. William W. O'Neill.)

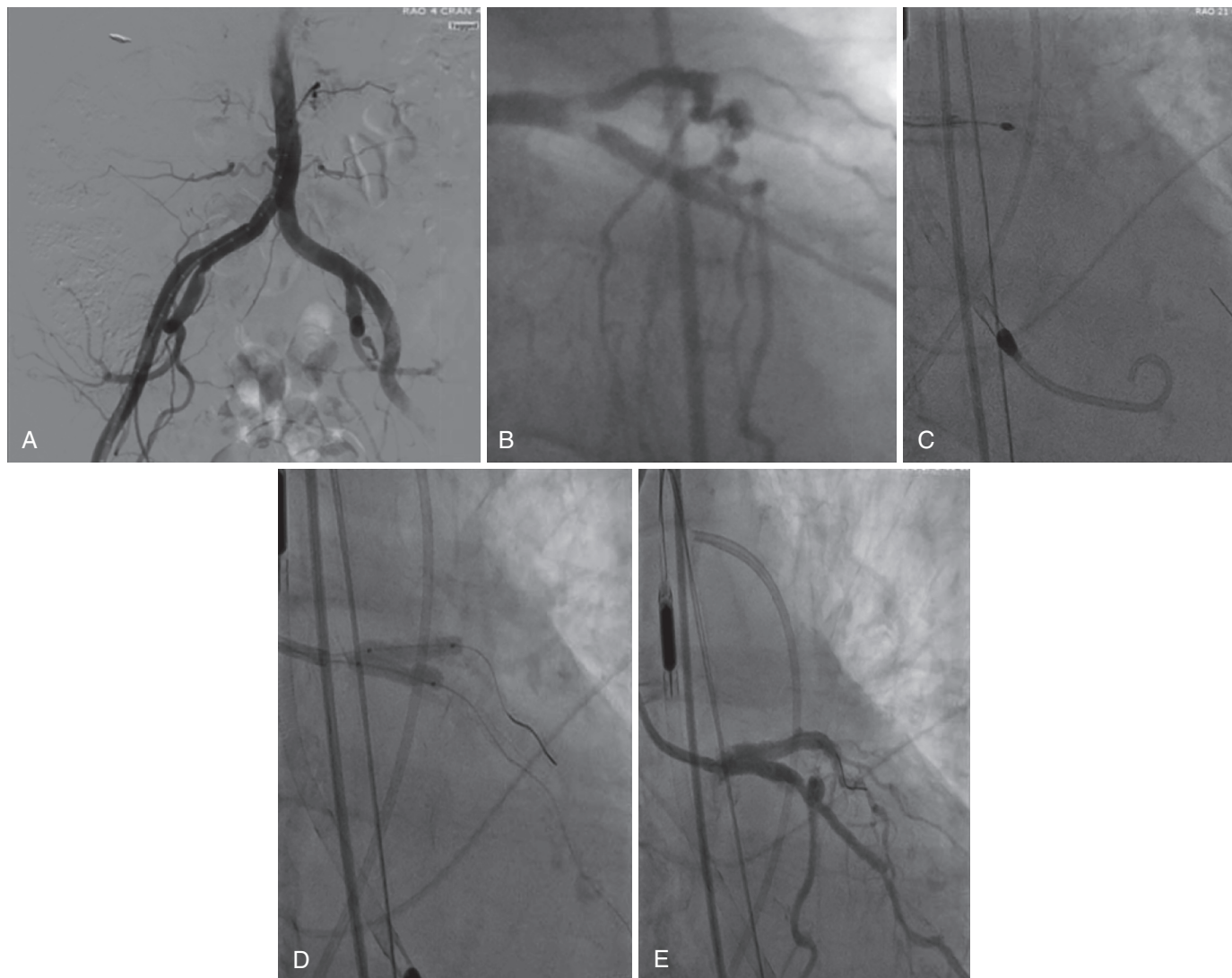


FIGURE 5.24 High-risk percutaneous coronary intervention procedure. **A**, Abdominal angiogram demonstrates that both femoral vessels are of adequate caliber for intervention. **B**, Preprocedure angiogram shows a highly calcified bifurcation distal left main coronary artery (LMCA) lesion. **C**, Angiogram showing the use of rotational atherectomy in the LMCA, left anterior descending coronary artery (LAD), and circumflex vessels. **D**, Simultaneous balloon inflation in the LAD and left circumflex coronary artery (LCX). **E**, Final angiogram after stent implantations in the LAD, LCX, and LMCA. (Courtesy of Dr. William W. O'Neill.)

baseline (Figure 5.24). Finally, stent deployment occurred in the LAD, OM, and bifurcation left main vessels. The final angiogram demonstrated wide angiographic patency of the three treated vessels (Video 5.7). Impella was removed immediately after intervention (Video 5.8), and hemostasis was achieved with suture closure.

This case exemplifies the principles of hemodynamic support for HRPPI. First, this older, highly symptomatic woman was deemed ineligible for CABG. Thus, either an HRPPI or hospice care was available. After a decision for intervention was reached, hemodynamic support was indicated because of the complex anatomy and poor LV function. In addition, the heavily calcified vessels mandated use of rotational atherectomy. Technical aspects of the case were complex; initially, even wire manipulation could cause cardiac collapse without support. Next, the use of atherectomy could cause coronary to reflow, which could be catastrophic. Extensive stenting of multiple vessels was required, and meticulous complex stenting guided by IVUS was also required

to complete this procedure. Even when coronary blood flow was abolished during simultaneous balloon inflation, the patient remained alert and communicative, with a stable cardiac rhythm. In this fashion, a careful, complete, and methodical coronary intervention could be performed.

COMPLICATIONS OF IMPELLA

Like all invasive devices, complications with use of Impella have been reported. The most worrisome complications arise from femoral access. The 13- to 14-Fr sheath is inserted in the femoral artery and can cause injury, requiring surgical repair. Proper preprocedure angiography and guided arterial puncture of the common femoral artery should minimize this risk. In the PROTECT II study,⁸ vascular surgery was required in 1.4% of IABG- and 0.9% of Impella-treated patients ($P = \text{NS}$). This complication thus should be quite uncommon.

If the device is left in place, a peel-away sheath is removed, and an occluder device is advanced so that only the 9-Fr shaft of the Impella remains in the femoral artery. It is essential to immobilize the instrumented leg so that catheter dislodgment does not occur.

The most common complication with prolonged support is catheter migration. Pressure alarms should detect this. Catheter repositioning using echocardiographic or fluoroscopic guidance may be required. If the inlet part is entrapped in a papillary muscle, high shear rates can occur, and hemolysis may develop. Hemolysis is rare during short-term support. Hemolysis occurred in 21% of the patients treated with Impella in PROTECT II. Tanawuttiwat and Chaparro⁷¹ reported a case of fiber wrapped around the inlet part of an Impella device, which led to severe hemolysis. Elhoussein and Hutchison⁷² reported placement of an Impella 5.0 for support, which led to flail mitral leaflet and severe mitral regurgitation. Conversely, Toggweiler et al.⁷³ reported a case where the Impella catheter migrated, and the shaft was lying on the anterior leaflet of the mitral valve. Functional mitral stenosis occurred as a result.

Ranc et al.⁷⁴ reported acute thrombosis of the inlet part of an Impella 5.0 that was inserted to manage a patient in cardiogenic shock. They theorized that the acute thrombosis that occurred 27 hours after implantation was related to subtherapeutic anticoagulation or entrapment of an intraventricular thrombus. These reports highlight the vigilance that is required for optimal safety of use. Patients must be therapeutically anticoagulated to avoid thrombotic complications and thrombosis of the inlet

shaft. Careful echocardiographic screening should occur to avoid use of the device when LV thrombus is present. Careful positioning of the catheter in the ventricle with intermittent checks to assure optimal position should occur after placement. Often slight withdrawal is needed soon after device activation.

When the device is left in place, daily chest radiography and daily echocardiography should be performed. Interference of mitral valve function should be considered if hemodynamic instability occurs. Repositioning of the device is ideally performed with fluoroscopy. With these precautions, excellent durable support of cardiac output can be safely achieved.

CONCLUSION: FUTURE ADVANCES

Now that best practices and optimal vascular management are widespread the concept of Impella-assisted HRPPI must be again formally tested. The PROTECT IV randomized trial will accomplish this. The trial (NCT04763200) is a prospective randomized trial in patients with ventricular dysfunction (LVEF <40%) and multivessel CAD (Figure 5.25). The local heart team will deem them eligible for HRPPI. Patients not in Shock or ST-segment elevation myocardial infarction will be enrolled. A trial of 1252 patients will be enrolled. Co-primary endpoints are incidence of death, stroke, durable LVAD, heart transplant, or rehospitalization (or cardiovascular causes at 3 years), and the second co-primary endpoint is death or NYHA Class III or IV at 1 year.

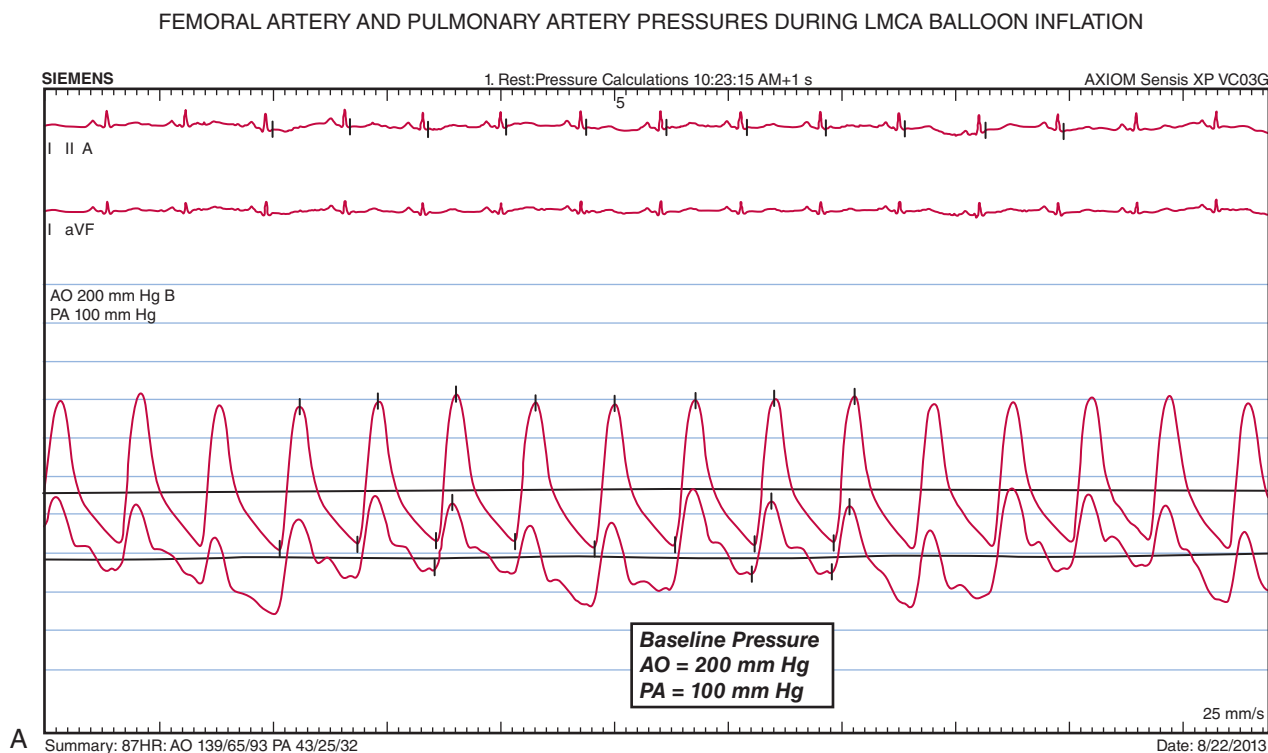


FIGURE 5.25 Femoral artery and pulmonary artery pressures during left main coronary artery balloon inflations. Baseline aortic (AO) and pulmonary artery (PA) pressures are recorded (A). As balloons are inflated in both the left anterior descending coronary artery and left circumflex coronary artery

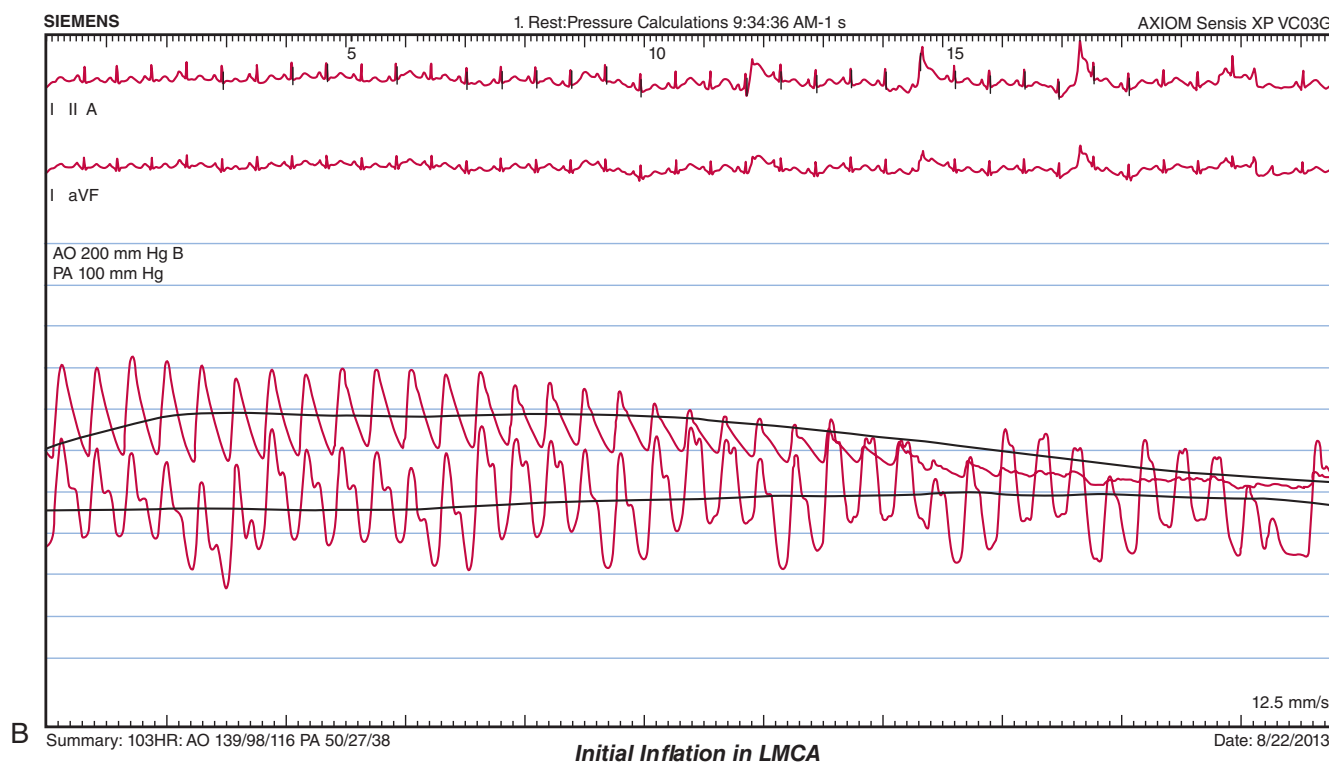


FIGURE 5.25, cont'd (B), aortic pulse pressure diminishes, yet mean aortic pressure is maintained at 100 mm Hg. There is very little difference in pulmonary artery pressure or contour. Immediately after balloon deflation (*lower panel*), the aortic and pulmonary artery pressures normalize. (Courtesy of Dr. William W. O'Neill.)

Mechanical circulatory support has provided a powerful tool for physicians to treat high-risk patients solely in the catheterization laboratory. Understanding the philosophy of these devices and developing skill sets to optimally use these devices are essential to achieve optimal outcome.

REFERENCES

1. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med*. 1979;301(2):61-68.
2. Mullin SM, Passamani ER, Mock MB. Historical background of the National Heart, Lung, and Blood Institute registry for percutaneous transluminal coronary angioplasty. *Am J Cardiol*. 1984;53(12):3C-6C.
3. Morrison DA, Sethi G, Sacks J, et al. A multicenter, randomized trial of percutaneous coronary intervention versus bypass surgery in high-risk unstable angina patients. The AWESOME (Veterans Affairs Cooperative Study #385, angina with extremely serious operative mortality evaluation) investigators from the Cooperative Studies Program of the Department of Veterans Affairs. *Control Clin Trials*. 1999;20(6):601-619.
4. Sharma S, Lumley M, Perera D. Intra-aortic balloon pump use in high-risk percutaneous coronary intervention. *Curr Opin Cardiol*. 2013;28(6):671-675.
5. Vogel RA, Shawl F, Tommaso C, et al. Initial report of the National Registry of Elective Cardiopulmonary Bypass Supported Coronary Angioplasty. *J Am Coll Cardiol*. 1990;15(1):23-29.
6. Teirstein PS, Vogel RA, Dorros G, et al. Prophylactic versus standby cardiopulmonary support for high risk percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol*. 1993;21(3):590-596.
7. Keelan PC, Johnston JM, Koru-Sengul T, et al. Comparison of in-hospital and one-year outcomes in patients with left ventricular ejection fractions < or =40%, 41% to 49%, and > or =50% having percutaneous coronary revascularization. *Am J Cardiol*. 2003;91(10):1168-1172.
8. O'Neill WW, Kleiman NS, Moses J, et al. A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: the PROTECT II study. *Circulation*. 2012;126(14):1717-1727.
9. Perera D, Stables R, Thomas M, et al. Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2010;304(8):867-874.
10. Rouleau J, Boerboom LE, Surjadhana A, et al. The role of autoregulation and tissue diastolic pressures in the transmural distribution of left ventricular blood flow in anesthetized dogs. *Circ Res*. 1979;45(6):804-815.
11. Nellis SH, Liedtke AJ, Whitesell L. Small coronary vessel pressure and diameter in an intact beating rabbit heart using fixed-position and free-motion techniques. *Circ Res*. 1981;49(2):342-353.
12. Marcus ML. *The Coronary Circulation in Health and Disease*. McGraw-Hill; 1983.
13. Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ Res*. 1973;32(3):314-322.
14. Burkhoff D. Pressure-volume loops in clinical research: a contemporary view. *J Am Coll Cardiol*. 2013;62(13):1173-1176.
15. Mendoza DD, Cooper HA, Panza JA. Cardiac power output predicts mortality across a broad spectrum of patients with acute cardiac disease. *Am Heart J*. 2007;153(3):366-370.
16. Burkhoff D, Naidu SS. The science behind percutaneous hemodynamic support: a review and comparison of support strategies. *Cathet Cardiovasc Interv*. 2012;80(5):816-829.
17. Williams DO, Korr KS, Gewirtz H, et al. The effect of intra-aortic balloon counterpulsation on regional myocardial blood flow and oxygen consumption in the presence of coronary artery stenosis in patients with unstable angina. *Circulation*. 1982;66(3):593-597.
18. Yoshitani H, Akasaka T, Kaji S, et al. Effects of intra-aortic balloon counterpulsation on coronary pressure in patients with stenotic coronary arteries. *Am Heart J*. 2007;154(4):725-731.
19. Kern MJ, Aguirre FV, Tatineni S, et al. Enhanced coronary blood flow velocity during intra-aortic balloon counterpulsation in critically ill patients. *J Am Coll Cardiol*. 1993;21(2):359-368.
20. Kern MJ, Aguirre F, Bach R, et al. Augmentation of coronary blood flow by intra-aortic balloon pumping in patients after coronary angioplasty. *Circulation*. 1993;87(2):500-511.
21. Burkhoff D, Cohen H, Bruckhorst C, et al. A randomized multicenter clinical study to evaluate the safety and efficacy of the TandemHeart percutaneous ventricular assist device versus conventional therapy with intra-aortic balloon pumping for treatment of cardiogenic shock. *Am Heart J*. 2006;152(3):469.e1-8.
22. van den Brink FS, Meijers TA, Hofma SH, et al. Prophylactic veno-arterial extracorporeal membrane oxygenation in patients undergoing high-risk percutaneous coronary intervention. *Neth Heart J*. 2020;28(3):139-144.

23. Kim MC, Ahn Y, Cho KH, et al. Benefit of extracorporeal membrane oxygenation before revascularization in patients with acute myocardial infarction complicated by profound cardiogenic shock after resuscitated cardiac arrest. *Korean Circ J*. 2021;51(6):533-544.
24. Lemor A, Hosseini Dehkordi SH, Basir MB, et al. Impella versus extracorporeal membrane oxygenation for acute myocardial infarction cardiogenic shock. *Cardiovasc Revasc Med*. 2020;21(12):1465-1471.
25. Banning AS, Adriaenssens T, Berry C, et al. Veno-arterial extracorporeal membrane oxygenation (ECMO) in patients with cardiogenic shock: rationale and design of the randomised, multicentre, open-label EURO SHOCK trial. *EuroIntervention*. 2021;16(15):e1227-e1236.
26. Singh-Kucukarslan G, Raad M, Al-Darzi W, et al. Hemodynamic effects of left-atrial venous arterial extra-corporeal membrane oxygenation (LAVA-ECMO). *ASAIO J*. 2022;68(9):e148-e151.
27. Chiang M, Gonzalez PE, O'Neill BP, et al. Left atrial venoarterial extracorporeal membrane oxygenation for acute aortic regurgitation and cardiogenic shock. *JACC Case Rep*. 2022;4(5):276-279.
28. Kent KM, Bentivoglio LG, Block PC, et al. Percutaneous transluminal coronary angioplasty: report from the Registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol*. 1982;49(8):2011-2020.
29. Laird JD, Madras PN, Jones RT, et al. Theoretical and experimental analysis of the intra-aortic balloon pump. *Trans Am Soc Artif Intern Organs*. 1968;14:338-343.
30. Voudris V, Marco J, Morice MC, et al. "High-risk" percutaneous transluminal coronary angioplasty with preventive intra-aortic balloon counterpulsation. *Cathet Cardiovasc Diagn*. 1990;19(3):160-164.
31. Kahn JK, Rutherford BD, McConahay DR, et al. Supported "high risk" coronary angioplasty using intraaortic balloon pump counterpulsation. *J Am Coll Cardiol*. 1990;15(5):1151-1155.
32. Hartzler GD. Percutaneous transluminal coronary angioplasty in multivessel disease. *Cathet Cardiovasc Diagn*. 1983;9(6):537-541.
33. Holmes DR Jr, Detre KM, Williams DO, et al. Long-term outcome of patients with depressed left ventricular function undergoing percutaneous transluminal coronary angioplasty. The NHLBI PTCA Registry. *Circulation*. 1993;87(1):21-29.
34. Briguori C, Airolidi F, Chieffo A, et al. Elective versus provisional intraaortic balloon pumping in unprotected left main stenting. *Am Heart J*. 2006;152(3):565-572.
35. Mishra S, Chu WW, Torguson R, et al. Role of prophylactic intra-aortic balloon pump in high-risk patients undergoing percutaneous coronary intervention. *Am J Cardiol*. 2006;98(5):608-612.
36. Curtis JP, Rathore SS, Wang Y, et al. Use and effectiveness of intra-aortic balloon pumps among patients undergoing high risk percutaneous coronary intervention: insights from the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes*. 2012;5(1):21-30.
37. Perera D, Stables R, Clayton T, et al. Long-term mortality data from the balloon pump-assisted coronary intervention study (BCIS-1): a randomized, controlled trial of elective balloon counterpulsation during high-risk percutaneous coronary intervention. *Circulation*. 2013;127(2):207-212.
38. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med*. 1999;341(9):625-634.
39. Shawl FA, Domanski MJ, Wish MH, et al. Percutaneous cardiopulmonary bypass support in the catheterization laboratory: technique and complications. *Am Heart J*. 1990;120(1):195-203.
40. Schreiber TL, Kodali UR, O'Neill WW, et al. Comparison of acute results of prophylactic intraaortic balloon pumping with cardiopulmonary support for percutaneous transluminal coronary angioplasty (PCTA). *Cathet Cardiovasc Diagn*. 1998;45(2):115-119.
41. Stack RK, Pavlides GS, Miller R, et al. Hemodynamic and metabolic effects of venoarterial cardiopulmonary support in coronary artery disease. *Am J Cardiol*. 1991;67(16):1344-1348.
42. Pavlides GS, Hauser AM, Stack RK, et al. Effect of peripheral cardiopulmonary bypass on left ventricular size, afterload and myocardial function during elective supported coronary angioplasty. *J Am Coll Cardiol*. 1991;18(2):499-505.
43. Thiele H, Lauer B, Hambrecht R, et al. Reversal of cardiogenic shock by percutaneous left atrial-to-femoral arterial bypass assistance. *Circulation*. 2001;104(24):2917-2922.
44. Aragon J, Lee MS, Kar S, et al. Percutaneous left ventricular assist device: "TandemHeart" for high-risk coronary intervention. *Cathet Cardiovasc Interv*. 2005;65(3):346-352.
45. Vranckx P, Otten A, Schultz C, et al. Assisted circulation using the TandemHeart, percutaneous transseptal left ventricular assist device, during percutaneous aortic valve implantation: the Rotterdam experience. *EuroIntervention*. 2009;5(4):465-469.
46. Schwartz BG, Ludeman DJ, Mayeda GS, Kloner RA, Economides C, Burstein S. High-risk percutaneous coronary intervention with the TandemHeart and Impella devices: a single-center experience. *J Invasive Cardiol*. 2011 Oct;23(10):417-24. PMID: 21972160.
47. Kovacic JC, Nguyen HT, Karajgikar R, et al. The Impella Recover 2.5 and TandemHeart ventricular assist devices are safe and associated with equivalent clinical outcomes in patients undergoing high-risk percutaneous coronary intervention. *Cathet Cardiovasc Interv*. 2013;82(1):E28-E37.
48. Scholz KH, Figulla HR, Schweda F, et al. Mechanical left ventricular unloading during high risk coronary angioplasty: first use of a new percutaneous transvalvular left ventricular assist device. *Cathet Cardiovasc Diagn*. 1994;31(1):61-69.
49. Frazier OH, Wampler RK, Duncan JM, et al. First human use of the Hemopump, a catheter-mounted ventricular assist device. *Ann Thorac Surg*. 1990;49(2):299-304.
50. Panos A, Kalangos A, Urban P. High-risk PTCA assisted by the Hemopump 14F: the Geneva experience. *Schweiz Med Wochenschr*. 1999;129(42):1529-1534.
51. Dubois-Rande JL, Teiger E, Garot J, et al. Effects of the 14F hemopump on coronary hemodynamics in patients undergoing high-risk coronary angioplasty. *Am Heart J*. 1998;135(5 Pt 1):844-849.
52. Vercaemst L, Vandezande E, Janssens P, et al. Impella: a miniaturized cardiac support system in an era of minimal invasive cardiac surgery. *J Extra Corp Technol*. 2002;34(2):92-100.
53. Meyns B, Dens J, Sergeant P, et al. Initial experiences with the Impella device in patients with cardiogenic shock—Impella support for cardiogenic shock. *Thorac Cardiovasc Surg*. 2003;51(6):312-317.
54. Dens J, Meyns B, Hilgers RD, et al. First experience with the Impella Recover(R) LP 2.5 micro axial pump in patients with cardiogenic shock or undergoing high-risk revascularisation. *EuroIntervention*. 2006;2(1):84-90.
55. Valgimigli M, Steendijk P, Sianos G, et al. Left ventricular unloading and concomitant total cardiac output increase by the use of percutaneous Impella Recover LP 2.5 assist device during high-risk coronary intervention. *Cathet Cardiovasc Interv*. 2005;65(2):263-267.
56. Rimmelink M, Sjaauw KD, Henriques JP, et al. Effects of left ventricular unloading by Impella Recover LP2.5 on coronary hemodynamics. *Cathet Cardiovasc Interv*. 2007;70(4):532-537.
57. Rimmelink M, Sjaauw KD, Henriques JP, et al. Effects of mechanical left ventricular unloading by Impella on left ventricular dynamics in high-risk and primary percutaneous coronary intervention patients. *Cathet Cardiovasc Interv*. 2010;75(2):187-194.
58. Henriques JP, Rimmelink M, Baan J Jr, et al. Safety and feasibility of elective high-risk percutaneous coronary intervention procedures with left ventricular support of the Impella Recover LP 2.5. *Am J Cardiol*. 2006;97(7):990-992.
59. Sjaauw KD, Konorza T, Erbel R, et al. Supported high-risk percutaneous coronary intervention with the Impella 2.5 device the Europella registry. *J Am Coll Cardiol*. 2009;54(25):2430-2434.
60. Dixon SR, Henriques JP, Mauri L, et al. A prospective feasibility trial investigating the use of the Impella 2.5 system in patients undergoing high-risk percutaneous coronary intervention (The PROTECT I Trial): initial U.S. experience. *JACC Cardiovasc Interv*. 2009;2(2):91-96.
61. Cohen MG, Ghatk A, Kleiman NS, et al. Optimizing rotational atherectomy in high-risk percutaneous coronary interventions: insights from the PROTECT II study. *Cathet Cardiovasc Interv*. 2014;83(7):1057-1064.
62. Henriques JP, Ouweneel DM, Naidu SS, et al. Evaluating the learning curve in the prospective Randomized Clinical Trial of hemodynamic support with Impella 2.5 versus Intra-Aortic Balloon Pump in patients undergoing high-risk percutaneous coronary intervention: a prespecified subanalysis of the PROTECT II study. *Am Heart J*. 2014;167(4):472-479.e5. doi:10.1016/j.ahj.2013.12.018.
63. Dangas GD, Kini AS, Sharma SK, et al. Impact of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump on prognostically important clinical outcomes in patients undergoing high-risk percutaneous coronary intervention (from the PROTECT II randomized trial). *Am J Cardiol*. 2014;113(2):222-228.
64. Stone GW, Mehran R, Dangas G, et al. Differential impact on survival of electrocardiographic Q-wave versus enzymatic myocardial infarction after percutaneous intervention: a device-specific analysis of 7147 patients. *Circulation*. 2001;104(6):642-647.
65. Kovacic J, Kini A, Banerjee S, et al. TCT-445 patients with 3-vessel coronary artery disease and impaired LVEF undergoing PCI with Impella 2.5 hemodynamic support have improved 90-day outcomes compared to intra-aortic balloon pump: a substudy of the PROTECT II trial. *J Am Coll Cardiol*. 2013;62(18 Supplement 1):B137-B137.
66. Hochman JS, Sleeper LA, White HD, et al. One-year survival following early revascularization for cardiogenic shock. *JAMA*. 2001;285(2):190-192.
67. Flaherty MP, Pant S, Patel SV, et al. Hemodynamic support with a microaxial percutaneous left ventricular assist device (Impella) protects against acute kidney injury in patients undergoing high-risk percutaneous coronary intervention. *Circ Res*. 2017;120(4):692-700.
68. Vetrovec GW, Anderson M, Schreiber T. The cVAD registry for percutaneous temporary hemodynamic support: a prospective registry of Impella mechanical circulatory support use in high-risk PCI, cardiogenic shock, and decompensated heart failure. *Am Heart J*. 2018;199:115-121.
69. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol*. 2004;44(7):1393-1399.

70. O'Neill WW, Anderson M, Burkhoff D, et al. Improved outcomes in patients with severely depressed LVEF undergoing percutaneous coronary intervention with contemporary practices: impella-supported high-risk percutaneous coronary intervention in patients with severely depressed LVEF. *Am Heart J.* 2022;248:139-149.
71. Tanawuttiwat T, Chaparro SV. An unexpected cause of massive hemolysis in percutaneous left ventricular assist device. *Cardiovasc Revasc Med.* 2013; 14(1):66-67.
72. Elhussein TA, Hutchison SJ. Acute mitral regurgitation: unforeseen new complication of the Impella LP 5.0 ventricular assist device and review of literature. *Heart Lung Circ.* 2014;23(3):e100-e104.
73. Toggweiler S, Jamshidi P, Erne P. Functional mitral stenosis: a rare complication of the Impella assist device. *Eur J Echocardiogr.* 2008;9(3):412-413.
74. Ranc S, Sibellas F, Green L. Acute intraventricular thrombosis of an Impella LP 5.0 device in an ST-elevated myocardial infarction complicated by cardiogenic shock. *J Invasive Cardiol.* 2013;25(1):E1-E3.



6 Radiation Safety In The Cardiac Catheterization Laboratory

LLOYD W. KLEIN

BASIC PRINCIPLES, 102

Physics of X-rays, 102
Principles of Radiation Safety, 103

OPERATION OF X-RAY FLUOROSCOPIC EQUIPMENT, 103

X-ray Generator, 103
C-Arm, 103
X-ray Tube, 103
Focal Spot, 104
X-ray Filtration, 104
Image Detector, 104
Automatic Dose Rate Control, 104
Image Display Monitor, 104
Operating Consoles, 105

FLUOROSCOPIC MODES, 105

FLUOROSCOPIC IMAGE QUALITY, 105

Spatial Resolution, 105
Contrast Resolution, 105
Temporal Resolution, 106
Noise, 106

ASSESSMENT OF RADIATION DOSE, 106

Expected and Limiting Radiation
Doses, 107

RADIATION-INDUCED INJURY, 108

Deterministic Risk, 108
Pregnancy, 109

RADIATION REDUCTION IN THE CATHETERIZATION LABORATORY, 109

Time, 110
Distance, 110
Collimation, 110
Dose Management, 110
Angulation, 111
Shielding, 111

OCCUPATIONAL HAZARDS OF THE CATHETERIZATION LABORATORY, 113

Orthopedic Injuries, 113
Cardiovascular Risk, 113

THE CATHETERIZATION LABORATORY OF THE FUTURE, 113

The essential purpose of fluoroscopic imaging is to obtain optimal real-time visualization of cardiac structures to make a diagnosis and to perform an intervention. The use of x-rays should be thought of as a tool that interventionists use to guide their performance of a procedure and the catheterization laboratory as their instrument. The safe and effective use of x-rays requires a working knowledge of the design and function of the catheterization laboratory, knowledge of the physics of x-rays, and the discipline to use preventive safety measures for the protection of the patient and laboratory staff.¹⁻⁵ Proficient technical skill entails comprehension of how to produce the best possible images while reducing radiation exposure, which is a hallmark of an expert interventional cardiologist. Additionally, recent attention has been given to the occupational health hazards posed by protective devices worn by personnel in the laboratory environment.⁶⁻⁸ This chapter outlines the principles of safe and effective radiation practice for patients, physicians, and staff in the interventional suite.

BASIC PRINCIPLES

Physics of X-rays

An x-ray instrument works generally by principles similar to those of a camera, but instead of capturing visible light, it uses differential x-ray photon absorption to create an image. The basic concept is that as x-rays travel through the patient's body, a portion is either absorbed or scattered by the atoms and molecules of internal structures based on their composition and density; the resulting modulation of beam intensity characterizes the structure.

A detector captures the residual transmitted x-rays; these are converted to electrical signals, which are recorded or further processed by computer. The resulting images, depicted in shades of gray, are derived from the concentration of x-rays detected and displayed in small digital elements (pixels), thus portraying structure in high resolution.^{4,5}

X-rays are electromagnetic waves on the high frequency portion of the spectrum. Consequent to its dual wave-particle nature, x-rays are composed of high-energy photons produced when energized electrons release energy. Electrons may occupy different orbitals, or energy levels, depending on the quantity of energy it possesses. When an electron falls from a higher to a lower energy orbital, the energy is released in the form of a photon. The amount of energy contained in the photon depends on the relative energy difference between the orbitals. The photons produced will have different frequencies depending on the amount of energy released and the source substance. X-ray photons are high frequency, and thus x-ray production depends on a material capable of releasing high levels of energy.

When an x-ray photon strikes an atom or molecule within structures of the body, each tissue atom may absorb the photon's energy; when this occurs, the electron rises to a higher energy orbital. The x-ray photon might also collide with an atom and be deflected into a different direction without absorption (scatter) or pass through the organ (transmission), thus reaching the detector. How much is absorbed or scattered versus transmitted creates a nonuniform beam, and this pattern is converted to an image, displayed in digital grayscale. The quantity of x-ray absorption defines the density of the shadow produced and thus characterizes the tissue. X-ray absorption is

increased proportionately to the third power of the atomic number. Bone has relatively high x-ray absorption because calcium has a higher atomic number than aqueous tissues; hence, whereas bone causes a dark shadow, water has low absorption and a light shadow.

With sufficient energy, absorption of the x-ray photon may cause the electron to leave the atom, creating a charged ion; for this reason, it is classified as “ionizing radiation.” This descriptor indicates the potential to permanently injure tissue or lead to neoplasm (if DNA is damaged).

Principles of Radiation Safety

Thus, x-rays provide the means to deliver innovative treatments to our patients but also have the capability of causing harmful effects, especially at high levels of exposure, if strict safety measures are not enforced. Two principles of radiation protection should be observed: (1) reduce ionizing radiation exposure to **as low as reasonably achievable** (ALARA) and (2) assure that the procedure is justified and that patients exposed to radiation may derive prospective benefit from the procedure to offset the risk. Optimization of delivered dose acknowledges the potential risk of any radiation. Appropriate dose management is required in all procedures involving ionizing radiation.^{1,2,9}

Three critical concepts underpin ALARA^{4,5}:

- There is no totally safe dose of ionizing radiation.
- The smaller the dose, the lower the risk of adverse effects.
- Incremental radiation exposure poses cumulative effects.

Scatter radiation is the foremost source of radiation exposure to physicians and staff.^{3,4} Scatter radiation is produced when the x-ray beam is deflected by the patient's body tissues, causing the x-rays to be dispersed (Compton effect). Scatter radiation spreads in diverse directions within the fluoroscopy suite during x-ray procedures.^{3,10}

OPERATION OF X-RAY FLUOROSCOPIC EQUIPMENT

To understand the proper conduct of x-ray imaging procedures and adherence to safety measures, it is necessary to be familiar with the operations of the fluoroscopic equipment.^{4,5} A fluoroscope generates x-rays to provide real-time radiographic imaging (Figure 6.1). Standard catheterization laboratory design is composed of a *generator*, *C-arm*, *x-ray tube*, *image detector*, and *operating console*. The radiographic images produced are processed digitally and displayed on a *flat-screen monitor*.

X-ray Generator

An x-ray generator contains an x-ray tube that produces the x-rays and a dedicated electrical system to create a current to the cathode.

C-Arm

The x-ray tube and image detector are mounted in a fixed orientation, so the tube and the detector are 180 degrees separated on opposite poles of a C-arm, ensuring that a linear path is maintained at all angles. The tube is housed underneath the procedure table. The image detector is mounted on a gantry above the table, permitting the operator to raise or lower the detector. The C-arm gantry and supports may be mounted on the floor or ceiling.

C-arm gantries have rotation and angulation speed limits of 25 degrees per second. Proximity sensors slow or stop rotation near the patient or the x-ray table or when contact is made with the patient or another object.

X-ray Tube

An x-ray tube is a simple vacuum tube containing a circular anode (positive electrode) and a cathode with multiple

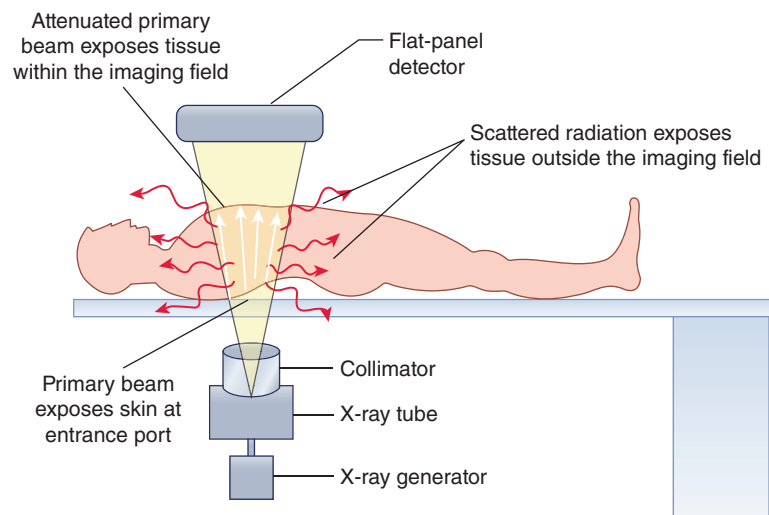


FIGURE 6.1. X-ray fluoroscopy system. X-rays enter the patient from the back. The primary beam exposes the subject only within the imaging field. The beam is collimated to a rectangular cross section and attenuated and scattered within the imaging field. Scatter radiation exposes structures within the subject remote from the imaging field. (Reproduced with permission from Hirshfeld JW Jr, Ferrari VA, Bengel FM, et al. ACC/HRS/NASCI/SCAI/SCCT expert consensus document on optimal use of ionizing radiation in cardiovascular imaging: best practices for safety and effectiveness: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2018;71:e283-351.)

filaments (negative electrode). The cathode emits a stream of electrons, and the anode collects the electrons. The assembly is composed of glass or metal.

An electric current is delivered from the x-ray generator to the cathode through the filament (a tungsten wire). Electrons are released by thermionic emission as the cathode temperature rises. These negatively charged electrons are accelerated across a large potential difference from the cathode toward the anode through a vacuum. The resulting electron stream is focused on the target surface of the rapidly rotating anode. The cathode focuses the electron stream so that it strikes a small area on the anode. The location of this collision forms x-ray spots of defined size and shape.

The anode generates x-rays, absorbs secondary electrons and scatter, and dissipates heat. When the electrons collide with the tungsten anode target, it produces heat (99%) and x-rays (<1%). The amount of heat produced is extremely large, requiring an oil-cooled system to disperse the heat. In part, the heat in the unit is also dissipated because of even distribution on a rotating surface, and the ceramic construction allows high heat capacity.

The emitted x-ray beam is then aimed from beneath the table through the patient. The housing permits only photons traveling in the direction of the patient to leave the enclosure, with minimal leakage (<1 mGy/h at 1 minute). The x-ray beam is composed of a discrete number of x-ray photons with variable energy; the maximum energy is limited by the tube voltage, which ranges between 60 and 150 kV.

The three most important x-ray tube characteristics are:

1. **MA (milliamperes):** The x-ray tube current, measured by the quantity of electrons traversing the anode-cathode gap each second. Tube current is proportional to x-ray output.
2. **Pulse width:** The duration of time that x-rays are acquired per frame or image. Shorter pulse widths produce better images of moving structures. The pulse width typically ranges from 6 to 10 msec. Pulse width is proportional to x-ray output.
3. **KVp (peak kilovoltage):** The voltage across the anode-cathode gap quantifies the range or spectrum of photon energies contained in the x-ray beam. The higher the kVp, the larger the mean photon energy, creating a more penetrating beam. The tube voltage is proportional to the square of x-ray output. Thus, a doubling of the KVp will quadruple x-ray output.

Focal Spot

The focal spot is the region on the anode on which the electron beam is focused and hence where x-rays are produced. Most commercial x-ray tubes have two (or more) focal spots, each with a dedicated cathode filament. The focal spot size can vary from 0.3 to 1.0 mm for cardiac angiographic systems. When the total heat produced exceeds the heat capacity of the anode, the focal spot changes to a larger size. This results in the distribution of the electrons over a larger anode area, lowering the temperature to avoid damage to the anode. X-ray image resolution is partially dependent on the size of the focal spot.

X-ray Filtration

Filtration is the removal of low-energy x-rays. Filtration reduces x-ray intensity and narrows the distribution of photon energies by removing those of the lowest energy. The maximum energy of the x-ray spectrum is unaltered, resulting in increased average photon energy ("beam hardening"). When low-energy x-ray photons are absorbed by superficial structures of the body, they contribute to patient dose but only minimally to image production. Consequently, after filtration, less radiation is needed to produce a given dose, which is therefore more penetrating. Thus, patient exposure and risk are reduced by beam hardening.

Image Detector

Digital *flat-panel detectors* are used in all modern catheterization laboratories. Digital flat-panel detectors convert x-rays into light, which is then transformed into an electric signal (via photodiodes) that is digitized. Direct conversion detectors provide high spatial resolution when coupled with small pixel sizes (80–200 μm). When the x-ray pulse has concluded, the stored information is amplified, digitized, and transmitted to a workstation. Conversion to grayscale images requires the flat screen to be linked to a television camera followed by an analog-to-digital conversion. The resultant information then undergoes processing to create an image before display.

Automatic Dose Rate Control

The automatic dose rate control (ADRC or automatic brightness control) acts as the central constituent of an electronic process that regulates x-ray parameters. Its function is to automatically adjust the components of the x-ray output, including mA, kVp, pulse width, filtration, and focal spot size, to optimize image quality. By this mechanism, correction is made for patient size, angulation, and attenuating structures. For example, shifting from shallow to steep angulations increases the effective patient depth; in response, the ADRC increases kVp, mA, or both to optimize image quality.

Image Display Monitor

After analog-to-digital conversion, images are displayed on an overhead television monitor. Modern monitors have diagonals ranging from 33 to 60 inches. The quality of the image should be evaluated for its luminance, grayscale fidelity, contrast resolution, and spatial linearity. Besides the monitor, other aspects of the display environment are vital, including:

- **Distance:** The ideal viewing distance between the operator and the monitor has changed with the advent of small guidewires. Monitors should be placed on the opposite side of the procedure table, directly across from the operators. Care should be taken that there are no obstructions to view (e.g., intravenous poles, ventilators) and that the monitor height is adjustable for best ergonomic support.
- **Viewing conditions:** Bright ambient lights increase glare on the image monitors, decreasing operator discernment

of variations in the grayscale. Modern catheterization laboratory designs provide overhead lighting that can be turned off or dimmed, supplemented by recessed lighting at the borders of the room.

Operating Consoles

The angiographer or technician uses a *tablesides console* to control movements of the C-arm, table, field of view, magnification, collimation, and detector height. The *foot pedal* is a switch to control the duration of x-ray exposure and x-ray mode (fluoroscopy or acquisition). An *operating console* in an adjacent *control room* provides the interface between the operator and the imaging and electrocardiographic and hemodynamic systems. The image display system also interacts with the PACS (Picture Archiving and Communication System) and the EMR (electronic medical record).

FLUOROSCOPIC MODES

The terms “fluoro” and “cine” denote two distinct modes of radiographic image display with divergent purposes.^{3,5,11} Consequently, they have dissimilar generator operation protocols and input x-ray doses, resulting in differences in image quality.

- *Acquisition* (or cine) describes the mode of operation used for recording high-resolution digital images. Cine necessitates higher input doses to optimize visualization and reduce noise. “Cine” describes the recording and playback of higher dose radiographic temporal still images (frames) of defined duration (pulse width) displayed as a loop. In modern laboratories, the acquisition rate is 15 frames/sec. Displaying a series of frames in sequence creates the perception of motion. The per-frame dose for acquisition is about 15 times greater than for fluoroscopy. Computerized digital presentation includes the processing, compression, storage, and display of such images. Cine is responsible for 60% of the total radiation exposure, despite only 5% of the total x-ray tube operation time, because of the higher energy requirement.
- *Fluoro* (or *fluoroscopy*) describes real-time dynamic imaging, in which a continuous x-ray image is displayed on a monitor so the movement of a catheter, guidewire, or contrast agent injection can be seen in detail. “Fluoro” denotes real-time observation with lower dose imaging, without the capability for recording. Fluoro is used in 95% of the total x-ray procedure time but causes only 40% of the total radiation exposure. This discrepancy is due to low doses and pulsing, which are noteworthy advances over the original use of continuous delivered energy or early pulsing methods at 30 frames/sec. Modern systems allow programmable pulsing adjustment: 15 frames/sec is now considered archaic; 7.5 (or 10) frames/sec is typical, usually with a low dose per frame rate (input dose 6.6 or 3.2 nGy/frame); and in some laboratories, low-dose pulsed fluoroscopy is at 3 frames/sec (which may reduce radiation exposure by 600% compared with standard-dose continuous fluoroscopy). The pulse duration is automatically adjusted and short

(3–10 msec), with no radiation between pulses, diminishing radiation exposure up to 50% in long cases. The neuropsychology of vision integrates the frames, so the images are seen in motion. Some laboratories have been hesitant to reduce acquisition rates because of concerns about impaired image quality, specifically image flicker and jerkiness; however, dynamic image processing, including image linking, which is routinely used in most modern x-ray systems, reduces flickering. Thus, greater noise is tolerable, and lower doses are effective. It is possible to store fluoro images, which saves exposure if high-quality images are not required.

FLUOROSCOPIC IMAGE QUALITY

Recognizing the intrinsic balance between “perfect” image quality and “safe” radiation dose is central to radiographic technique.^{3,5} Before measures that reduce radiation dose are implemented, it should be recognized that any such modification has the potential to decrease image quality. Current fluoroscopic x-ray systems provide multiple means of dose management, such as frame rate adjustment, virtual collimation, adjustable dose, last image hold, and real-time dose display.

Excellent image quality is contingent on several patient, procedural, and x-ray determinants. The inherent balance between image quality and radiation dose must be recognized. Moreover, the ADRC rapidly regulates dose in response to patient size and projection to optimize image quality. Moreover, fluoroscopic image quality is unavoidably affected by the interaction among spatial resolution, temporal resolution, contrast resolution, and noise. Modifications made to improve one parameter have the potential to adversely affect the others.

Spatial Resolution

Spatial resolution refers to the capability to differentiate fine detail on an image. It is defined as the smallest distance between two separate structures in close proximity. In digital imaging, the size of the pixel used usually determines this value. Resolution is critical in cardiac angiography: the perception of small vessels, fine guidewires, and anatomic boundaries depends on high resolution. Spatial resolution is also influenced by the focal spot size, geometric magnification, and motion. If the focal spot size is small, the edges of objects may appear blurred (“penumbra”). The location of the imaged object relative to the tube and detector may also impact the penumbra. An object located close to the source and away from the detector is magnified (*geometric magnification*), and therefore the penumbra increases.

Contrast Resolution

Contrast resolution is the capacity to detect differences in signal intensity (quantitated as pixel values), depicted in a visual image as shades of gray. The visual perception of shades of gray is less accurate than the quantitation actually provided by digital quantitation. Cardiovascular images

are displayed in 16 bits depth (256 shades of gray) arrayed with a resolution of 1024×1024 -pixel matrix. Experienced angiographers can perceive contrast disparities of approximately a 15% difference. Because the eye makes a logarithmic distinction to changes in brightness, contrast changes in the black range of the grayscale affect contrast perception more than in the white shades.

Contrast resolution allows the detection of small differences in brightness and attenuation. Distinguishing two objects of similar density is clinically beneficial, for instance, when differentiating detail in a contrast-filled artery overlying the spine or diaphragm.

Determinants of contrast resolution fall into three categories:

- *Subject*: depends on the object being imaged (composition, size) and the x-ray beam characteristics (kVp, filtration)
- *Detector*: depends on the type of detector and its response to radiation
- *Display*: depends on ambient lighting, monitor brightness and linearity, matrix size, and bit depth

Temporal Resolution

Motion of the object within one pulse duration may create a blurry (*motion blur*) image. Blur results when the object being recorded moves rapidly during the recording of a frame or single image; decreasing the pulse duration usually diminishes this appearance. Temporal resolution is the capacity of the imaging chain to resolve two events separated by time. A common example when blur might be observed is a right coronary angiogram in the right anterior oblique (RAO) view at rapid heart rates. Determinants include pulse width and the time between pulses. An acquisition acquired at 3 frames/sec will have a 10 times worse temporal resolution than another acquired at 30 frames/sec. Temporal resolution is independent of spatial resolution.

Noise

Noise is an irregular granular pattern in an image, appearing mottled, grainy, or snowy, that is random and not reflective of an actual structure. These densities degrade useful image information. The ability to distinguish a random signal is measured by the ratio of the differential intensity to the ambient noise level. This ratio is called the image *signal-to-noise ratio*. It is important to distinguish random noise effects from image artifacts, which are entirely separate considerations. Despite seeming to suggest randomness, the term *artifact* refers to undesirable image features that occur repeatedly and reproducibly under identical conditions.

There are three categories of noise:

1. *Quantum noise*: The most common form, quantum noise, or "mottle," is an intrinsic property of x-ray imaging. Quantum noise is proportional to the photon intensity (number of quanta) used to produce the image and is inversely proportional to the square root of the detector dose. Thus, to reduce the proportion of noise by half, the detector dose must be increased by a factor of 4. Postacquisition spatial and temporal filtering and other imaging processing techniques can

reduce quantum noise but may decrease spatial and temporal resolution.

2. *Detector (or electronic) noise*: Flat-panel detectors are prone to noise because of high sensitivity. These detectors contain various nonuniformities that are both structured and random in nature. Structured noise is a consequence of fixed nonuniformities in detector response, including variations in sensitivity and linearity. Random noise includes electronic noise and sporadic malfunctioning detector elements. Calibration and image processing can modify structured detector noise, but random noise cannot be systematically eliminated.
3. *Anatomic (or structural) noise*: This form of noise is secondary to high data density produced by surrounding tissues that conceals important structures and detail. The most common cause of anatomic noise is the presence of bone. At very high detector doses, anatomic noise can be more detrimental than quantum and detector noise.

The interrelationships among these parameters are complex. Increasing the kVp produces high-energy photons that transmit through contrast, decreasing noise but at the cost of potentially resulting in a "washed-out" image. Increasing the pulse width may result in motion blur. Increasing the mA results in better images but also increases scatter. Optimal balance maximizes the kVp to produce acceptable images, keeping the mA low and reducing exposure.

The use of digital magnification should be limited. Magnification of an image from a 7-inch field of view to 5-inch magnification increases peak skin dose (PSD) by nearly 50%. Although digital magnification increases the size display of the imaged anatomy, the concomitant increase in dose may require the use of a larger focal spot, which decreases spatial resolution.

Anatomic noise and some forms of detector noise can be significantly reduced by the process of subtracting one image from another. However, digital subtraction does not decrease quantum mottle because this form of noise is randomly distributed in both images.

Although subtraction angiography provides the advantage of removing anatomical noise, such as bone, it requires a marked increase in dose per frame. Accordingly, increased noise is produced in the subtracted image if standard radiation doses are used. Therefore, subtracted images necessitate an increased dose compared with unsubtracted images. This may require 10 to 20 times the dose/frame of standard-dose acquisition images. For this reason, low frame rates (3 to 4 frames/sec) are usually used with subtraction angiography to limit the radiation dose. Therefore, digital subtraction angiography should be restricted to situations when it is necessary.

ASSESSMENT OF RADIATION DOSE

Dose can be characterized by a number of quantitative measures of radiation exposure (Table 6.1).¹⁻⁵

Fluoroscopic time (FT, measured in minutes) is the time that fluoroscopy is used, not including acquisition imaging. For this reason, FT does not adequately connote patient radiation dose.¹⁻⁴

TABLE 6.1 Terminology of Radiation Doses

TYPE OF DOSE	SI UNIT	DEFINITION OR PURPOSE
Kerma (K)	Gray (Gy)	Sum of initial kinetic energies released in material per unit mass
Air kerma at IRP ($K_{a,r}$)	Gray (Gy)	Kerma in air at the IRP
Air kerma rate at IRP ($K_{a,r}$)	Gray/sec (Gy/s)	Instantaneous rate of air kerma at IRP
Air kerma area product (KAP or DAP)	Gy*cm ²	Air kerma × field size; indicative of stochastic risk
Absorbed dose (D)	Gray (Gy)	Mean energy/unit mass by ionizing radiation to a material
Peak skin dose ($D_{skin,max}$)	Gray (Gy)	Maximum absorbed dose at one skin area; indicates skin injury risk
Effective dose (ED)	Sievert (Sv)	Estimate of stochastic risk caused by x-ray exposure

DAP, Dose area product; IRP, the interventional reference plane; KAP, air kerma air product.

Absorbed dose (Gy) is the amount of energy absorbed by a volume of tissue divided by its mass; thus, the concentration of energy absorbed. **Kerma** (kinetic energy in matter) is another term used to describe the same concept.

Two standard parameters are reported on fluoroscopic systems: **total air kerma** (also called cumulative air kerma) at the interventional reference point ($K_{a,r}$, gray [Gy]) and **air kerma area product** (P_{KA} , Gy*cm²) (also called the dose area product [DAP]). These parameters quantitate the radiation dose delivered to the air and to body tissues. Measurement of procedure cumulative air kerma is required on interventional x-ray systems. $K_{a,r}$ is used to monitor patient dose burden because it is associated with deterministic effects. DAP is the product of air kerma and the cross-sectional area of the irradiating beam.

The effective dose (ED) (measured in millisieverts [mSv]) relates whole-body absorbed dose to stochastic risk. Its utility is to permit comparisons of risks among exposed individuals. P_{KA} is used to monitor the potential for stochastic effects. The ED may be estimated by multiplying DAP by a conversion factor based on type of procedure and the type of irradiated tissue. ED is not provided by x-ray equipment. ED can be thought of as the summation of equivalent doses to all organs, each adjusted to account for the sensitivity of the organ to radiation.

The PSD (measured in Grays) is the maximum dose received by an area of patient skin; PSD ($D_{skin,max}$) is the best indicator of radiation-induced cutaneous injury. As PSD increases, the likelihood and severity of deterministic skin effects increases. There is no currently available method to measure PSD in real time. PSD is determined mainly by the instantaneous dose rate and the duration of exposure of a specific skin segment.¹¹

Equivalent dose (measured in millisieverts) is the absorbed dose to an organ, adjusted to account for the effects of the type of radiation and its relative biological impact. It provides a relative dose that is used to measure radiation risk to a specific tissue. Equivalent dose is difficult to calculate but is biologically significant, representing stochastic risk.

Expected and Limiting Radiation Doses

The National Council on Radiation Protection and Measurements recommends an ED limit of 50 mSv/year and a cumulative lifetime limit of 10 mSv multiplied by age for radiation workers and 1 mSv/year for the patient.

Patient

The DAP is approximately 0.12 mSv/Gy*cm² for diagnostic coronary angiography and 0.18 to 0.28 mSv/Gy*cm² for coronary intervention. Modern cardiac procedures produce ED ranging 4 to 21 mSv for diagnostic and 9 to 29 mSv for interventional procedures, respectively. Coronary angiography and percutaneous coronary intervention (PCI) produce mean DAPs in the range 20 to 106 Gy*cm² and 44 to 143 Gy*cm², respectively. The average dose for the cardiologist per procedure is 0.05 mGy.¹²⁻¹⁴ Radiation exposure during transcatheter aortic valve replacement (TAVR) appears similar to that for PCI of moderate complexity¹⁵: the median radiation dose during TAVR is 1639 mGy (983–2420) or 188 (106–321) Gy*cm².

Patients likely to require higher than usual doses are obese, have complex disease, need a prolonged procedure, or have undergone a recent fluoroscopic procedure (e.g., previous 30–60 days). The operator should be notified by staff when $K_{a,r}$ exceeds 3 Gy and then every 1 Gy thereafter. The operator must consciously balance the risk with the benefits of proceeding when high doses of radiation are delivered.^{16,17} There is also variation in patient susceptibility, with older patients and those with fair skin, collagen vascular disease, diabetes, and hyperthyroidism most at risk for exaggerated reactions.¹⁸

The cardiac catheterization report should contain a statement of measured radiation parameters during the procedure: FT, $K_{a,r}$, and P_{KA} . When procedures using high radiation doses are performed, chart documentation of patient notification and communication with the primary care provider is advised.

Patients should be educated regarding potential skin changes (e.g., red patch on the back) when $K_{a,r}$ is greater than 5 Gy ($P_{KA} > 500$ Gy*cm²). A 30-day phone call follow-up and office visits may be necessary. A qualified physicist should promptly calculate PSD, and the involved skin examined at 2 to 4 weeks when $K_{a,r}$ is greater than 10 Gy ($P_{KA} > 1,000$ Gy*cm²). The Joint Commission identifies PSD greater than 15 Gy as a sentinel event; hospital risk management and regulatory agencies must be contacted within 24 hours. If skin tissue injury occurs, the dermatologist should be made aware of its potential radiation cause. A biopsy should be performed only if required because a biopsy site wound may lead to more problems than the radiation effects.

Operator

Operators are exposed to much smaller amounts of radiation than patients during each procedure but are exposed repeatedly, resulting in large lifetime exposure. Operator ED is less well studied than for patients, hindered by inconsistent use of personal dosimeters by operators. The ED per procedure ranges from 0.02 to 30.2 μ Sv for diagnostic catheterization, 0.17 to 31.2 μ Sv for PCI, 0.24 to 9.6 μ Sv for ablation, and 0.29 to 17.4 μ Sv for pacemaker or defibrillator



implantations. A busy interventional cardiologist using good technique and proper protective equipment has a per-procedure average ED of 8 to 10 μSv and receives 2 to 4 mSv/yr.¹⁻⁴

The International Commission on Radiological Protection (ICRP) has set dose limits for occupational exposure at an ED of 20 mSv per year, averaged over 5 years (limit of 100 mSv/5 years); 50 mSv in any single year; and an equivalent dose limit of 50 mSv for the lens in any single year, 500 mSv for the skin (average dose over 1 cm^2), and 500 mSv for the hands and feet.

Transradial procedures have been associated with increased radiation exposure to patients and operators, in part because the operator is located closer to the patient (the scatter source) and the x-ray source. However, careful attention to shielding and increased proficiency with radial technique probably reduce the exposure to that of femoral procedures in practice.^{19,20}

Dosimeters

The local radiation safety program is responsible to monitor staff and operator radiation dose through the use of personal dose monitors. Film badges are one type of personal radiation monitoring device. Thermoluminescent dosimeters (TLDs) are another common type. A TLD is composed of a phosphor-containing solid crystal structure that interacts with the ionizing radiation upon exposure. Other available dosimeters include optically stimulated luminescence (using radiation-sensitive aluminum oxide) and pocket dosimeters, including digital designs, which use Geiger counters.

It is the individual's responsibility to wear a dosimeter. Institutional enforcement of the monitor policy creates a safe occupational environment. Although a single dosimeter positioned on the collar is sufficient, two dosimeters—one at the waist underneath and one at the collar outside the protective garment—provides a better reflection of ED.¹ Regular review of personnel monitoring by formal quality processes assures the safe practice of radiation. Frequent excess exposure should be investigated, including how procedures are performed and whether the proper use of protective equipment is being used.^{1,18}

Some operators and staff use commercially available individual real-time dose monitoring devices to measure their personal exposure. Unquestionably, comprehensive monitoring of staff exposure is fundamental to continuous optimization of radiation safety. Whether individual real-time dosimetry provides incremental actionable information systemically compared with routine monitoring is unknown but may provide the wearer with enhanced radiation awareness and immediate feedback, allowing behavioral modification and a sense of personal control.¹⁹

RADIATION-INDUCED INJURY

The risks associated with fluoroscopic procedures are of concern to the patient and catheterization laboratory personnel. The potential risks of radiation exposure must be balanced against the benefits of invasive and interventional procedures. Radiation exposure has been linked

with malignancy, cataract formation, brain tumor, skin injury, and genetic defects.¹⁻⁵

Deterministic Risk

Deterministic effects are predictable phenomena with a clear dose-dependent relationship.¹⁸ There is a threshold dose for onset of injury, below which the injury does not occur. Each tissue has a unique threshold for injury. Both the probability and the severity of deterministic effects increase with doses in excess of the threshold. Examples of deterministic effects include cataracts; radiation-induced epilation; erythema; and skin injury, necrosis, and ulceration.

Skin

Multiple factors affect the sensitivity of the skin to radiation-induced injury, including fair skin, collagen diseases, malnutrition, steroids, diabetes mellitus, chemotherapeutics, and previous radiation exposure at the same site. Predicting the likelihood of radiation-induced skin injury with repeated exposures is complex and depends on the cumulative dose received and the length of time between exposures. However, there is a close relationship between absorbed dose and the effect on the skin (Table 6.2). As long as permanent skin injury has not been previously induced, it is likely that the exposed skin will recover completely, but this process occurs over a period of at least 6 months. Varying the tube angle when possible will change the location of the irradiated skin.¹¹

Minor transient skin erythema is not likely to occur unless $D_{\text{skin,max}}$ is greater than 2 Gy. Persistent or permanent hair loss or pigmentary changes are likely to occur only when $D_{\text{skin,max}}$ is greater than 5 Gy (Figure 6.2). Telangiectasias, dermal atrophy, and skin induration occur only when $D_{\text{skin,max}}$ is greater than 10 Gy. Skin necrosis and ulceration typically do not occur in healthy patients until the PSD is greater than 15 Gy.

These dose-related guidelines pertain only to the localized area of skin that has received doses of radiation exceeding these quantities. There are no official limits on the $D_{\text{skin,max}}$ that a patient may receive during diagnostic or interventional procedures. However, The Joint Commission has defined a “sentinel event” when the cumulative skin dose exceeds 15 Gy to a single field, which requires reporting to the institution's Quality Review Board. If a patient undergoes multiple high-dose angiographic procedures within a 6- to 12-month time frame, it is advisable to consult with a qualified medical physicist regarding the likelihood of radiation-induced skin injury before additional elective high-dose procedures.

TABLE 6.2 Skin Injury and Radiation Doses

EFFECT	ABSORBED DOSE (GY)	ONSET
Transient erythema, hair loss	2–3	Hours or weeks
Persistent erythema, hair loss	6–7	1–3 wk
Skin fibrosis, atrophy	10–11	1–3 mo
Wet skin loss	15	1 mo
Skin necrosis, ulceration	18+	2–5 mo



FIGURE 6.2 Radiation-induced skin injury. Left infrascapular telangiectasias and skin induration. Mildly pruritic, indurated skin with telangiectasias after five left coronary artery percutaneous intervention procedures. Another percutaneous intervention would carry a significant risk of severe skin injury in this area.

Eyes

Damage to the conjunctiva, iris, sclera, and blood vessels of the retina may result from high radiation doses. The lens is the most sensitive location; it is susceptible to irreversible damage from a relatively low dose of radiation with subsequent formation of cataracts. Radiation-induced cataracts can be differentiated from naturally occurring cataracts by their location in the posterior pole of the lens.

Stochastic Risk

Stochastic effects (also “probabilistic” effects) are non-threshold biologic effects of radiation that occur by chance. Injuries of this type occur on the basis of statistical probability and are an “all-or-none” phenomenon.¹⁸ The likelihood of stochastic injury is proportional to the radiation dose magnitude, but the severity of a stochastic injury is not. The currently accepted model of stochastic injury is the “linear no-threshold” model, which conceptualizes risk as linearly proportional to dose and presumes that there is no dose at which risk is not present. Stochastic risk is cumulative. Stochastic effects of radiation include neoplasm, malignancy, leukemia, and heritable genetic defects.

Certain organ tissues are particularly sensitive to radiation-induced malignancy. The organs with the greatest risk for cancer formation are the brain, skin, and thyroid. Others include the colon, stomach, breast, lung, and bone marrow. The period between radiation exposure and detection of malignancy varies greatly among different tissues and different patients—as little as 7 years for leukemia to 20 years or more for other malignancies.

The chance that fluoroscopic x-ray exposure during cardiac procedures might induce DNA damage and cause cancer or genetic defects is small. There is approximately a 1% increased lifetime risk of malignancy for every 1000 mSv of ED. The incremental fatal cancer risk is estimated at 5.5% per 1000 mSv, in addition to 21.2% incidence of cancer in the general population.

Pregnancy

Cardiac catheterization and interventions can be safely performed during pregnancy when the benefit of the procedure is greater than the small risk involved. As the ALARA principle states, there must be clinical justification that acknowledges the anticipated radiation exposure to the fetus.

The precise risk and known dangerous fetal radiation doses depend on the time of the procedure postconception. The general rule is that the risks are highest 8 to 15 weeks after conception, less at 16 to 25 weeks, and least likely in the third trimester. The fetal central nervous system and developing brain are most sensitive to radiation. During the time frame of less than 25 weeks postconception, fetal doses greater than 100 mGy are associated with cognitive effects, and doses greater than 1 Gy are highly associated with mental retardation. The risk of leukemia and malignancy is about the same as in children. According to the ICRP,¹⁹ termination of the pregnancy of fetal doses less than 100 mGy is unjustifiable, and those between 100 and 500 mGy require individual judgment.

The procedure should be performed in a manner that minimizes fetal exposure, which primarily results from scatter within the patient. Thus, collimation, angulation, fluoroscopy time, and x-ray output should be adjusted explicitly to reduce scatter and the radiation dose to the lower abdomen. The placement of a lead apron on the table beneath the patient or having the patient wear a lead apron to shield the fetus from the x-ray beam has very little effect.

Prudent use of usual radiation protection protects the fetus; pregnant operators and catheterization laboratory staff do not need to stop working or limit their time doing procedures. Standard lead aprons are sufficient to protect the embryo and fetus during fluoroscopic procedures.^{21,22}

RADIATION REDUCTION IN THE CATHETERIZATION LABORATORY

Interventional cardiologists are responsible for, and must be actively involved in, managing radiation dose in each case. Establishing a radiation safety-conscious environment improves patient, staff, and physician safety.^{1,5} The radiation dose received by patients and catheterization laboratory personnel during invasive procedures can vary considerably, even with the same procedure and similar patient size, depending on how the procedure is conducted (Table 6.3).^{1-5,16-18} The greatest source of occupational radiation exposure stems from radiation scatter from the patient and the table because the direct beam passes through them from the x-ray source to the image detector. For this reason, fluoroscopy suites are equipped with radiation shields of various forms, including mobile shields, table skirts, radiation absorption pads, and suspended shields or suspended aprons or a combination, designed to reduce scatter radiation from various regions of the operating suite.

Effective dose management strategies begin before the procedure and continue with the technique used while performing the procedure (Table 6.4). The interventional cardiologist is responsible for using good technique to

**TABLE 6.3 Procedure-Based Case Management of Radiation**

I. Preprocedure
A. Radiation safety program for catheterization laboratory
1. Dosimeter use, shielding, angulations
B. Imaging equipment and operator knowledge
1. On-screen dose assessment (AK, DAP)
2. Dose saving: store fluoroscopy, adjustable pulse and frame rate, and last image hold
C. Preprocedure dose planning
1. Assess patient and procedure, including patient's size and lesion(s) complexity and location.
D. Informed patient with appropriate consent
II. Procedure
A. Limit fluoroscopy: Step on pedal only when:
1. Looking at screen
2. Moving equipment or actively evaluating
B. Limit cineangiography:
C. Use fluoroscopy when high image quality not required.
D. Limit magnification, frame rate, steep angulation.
E. Use collimation and filters to fullest extent possible.
F. Vary tube angle when possible to change skin area exposed.
G. Consider position of table and image receptor:
1. X-ray tube too close to patient increases dose
2. High image receptor increases scatter
H. Keep patient and operator body parts out of field of view.
I. Maximize shielding and distance from x-ray source (for all personnel).
J. Manage and monitor dose in real time.
III. Postprocedure
A. Document radiation dose in records (FT, AK, DAP).
B. Notify patient and referring physician when high dose delivered.
1. AK >5 Gy: chart document; inform patient; arrange follow-up
2. AK >10 Gy: qualified physicist should calculate skin dose
3. PSD >15 Gy: TJC sentinel event
C. Assess and refer adverse skin effects to appropriate consultant

AK, Air kerma; DAP, dose area product; FT, fluoroscopy time; Gy, Gray; PSD, peak skin dose; TJC, The Joint Commission.
Adapted from Christopolous².

TABLE 6.4 Minimizing Radiation Exposure to the Patient

1. Minimize the number and duration of acquisitions and fluoroscopy time.
2. Decrease the fluoro and acquisition frame rates to as low as necessary.
3. Decrease the dose in fluoro and acquisition frames.
4. Minimize the distance of the patient to the image detector.
5. Maximize the source to skin distance to minimize magnification.
6. Minimize the C-arm angulation and use shallow angles when possible.
7. Vary the C-arm angulation to minimize repetitive exposure.
8. Exclude body parts outside the area of interest.
9. Use low-dose acquisition software or hardware.
10. Limit the use of digital magnification.
11. Actively collimate to the area of interest.
12. Minimize the use of subtraction angiography.
13. Carefully consider skin exposure in repeat interventions.

limit radiation exposure to the patient and catheterization laboratory staff. Reduction of patient radiation dose is likely to also reduce the dose to the operator and laboratory personnel.

Beyond patient dose reduction, there are three primary approaches that reduce occupational exposure: decrease the time near the radiation source, increase the distance from the source, and maximize the amount of shielding. Measures to reduce exposure to scatter can be divided into measures that are based on equipment configuration (e.g., architectural shielding, protective equipment, changing x-ray system parameters) and operator behavior modification (e.g., fluoroscopy use, position adjustment, radiation surveillance) (Table 6.5).

TABLE 6.5 Minimizing Occupational Radiation Exposure to the Operator and Laboratory Personnel

Time
1. Reduce the time near the source of radiation.
2. Reduce distance number of acquisitions to a minimum.
3. Minimize fluoroscopic time; use the distance pedal sparingly.
4. Minimize the time per frame.
Shielding
1. Maximize shielding during radiation exposure.
2. Avoid direct radiation exposure.
3. Use proper barriers to block radiation
4. Use all available shielding, barriers, and eyewear correctly
Distance
1. Inverse square law: radiation exposure decreases as a function of $1/d^2$
2. Increase the distance of the operator and laboratory personnel from the x-ray source.
3. Minimize C-arm angulations with the x-ray tube near the operator.
4. Enhanced awareness of the distances between the patient, the x-ray source, the source-to-image distance, and the operator and laboratory personnel.

Time

The average procedure time for a diagnostic coronary angiogram is 15 to 30 minutes, and a typical interventional procedure (PCI or electrophysiologic [EPS]/pacing) takes 60 to 120 minutes; these times are highly variable depending on procedure complexity and operator experience. The interventional cardiologist should make every effort to minimize fluoro and acquisition times.

Distance

Operator and staff should consciously maximize their distance from the x-ray tube. Maintaining distance is of particular importance in radial access cases.²⁰ The intensity of radiation exposure follows the *inverse square law*, meaning that exposure decreases with the square of the distance from the source ($1/d^2$). Thus, doubling the distance from the radiation source reduces exposure by a factor of $(1/2)^2$ or one-fourth.

Collimation

Collimation reduces the x-ray field of view, thereby decreasing the radiation dose to tissue outside the area of interest. This reduces scatter, which improves image quality and reduces occupational exposure. Collimation to the area of interest reduces DAP; however, it does not reduce the PSD in the area being irradiated. More scatter radiation is produced when the beam irradiates more tissue. High-kVp and low-mAs techniques will produce less scatter.

Dose Management

The operator should actively manage the dose delivered. Preprocedure planning is essential to ideal dose management. Patient characteristics suggesting an increased likelihood of high doses or prolonged procedures are obesity, complex disease, high risk or technically difficult procedures, or a recent fluoroscopic procedure (previous 30–60 days).

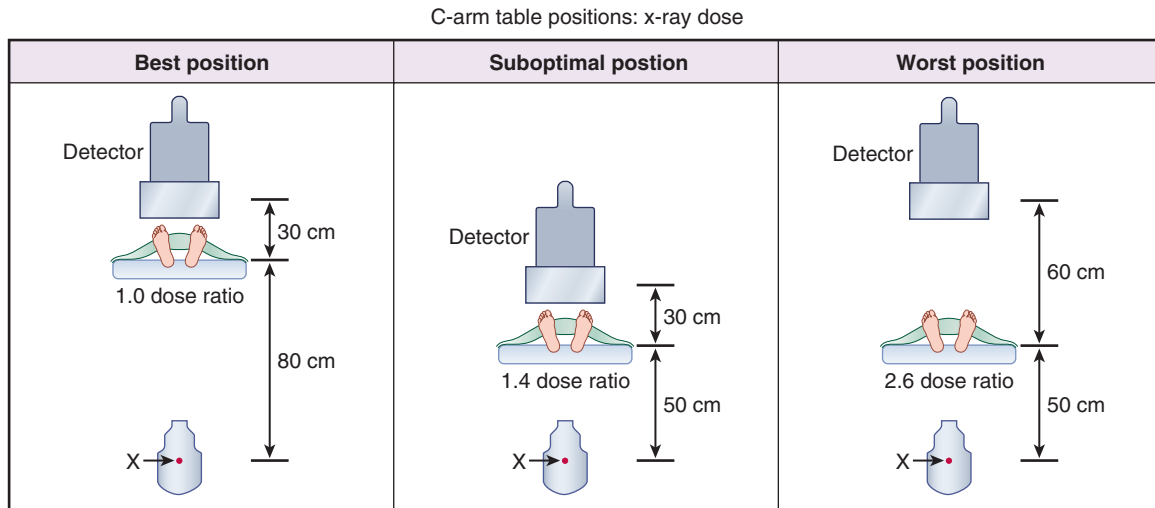


FIGURE 6.3 Relation of table height to skin entrance dose. Best position: the patient is located far from the x-ray source; the image detector is close to the patient. This position maximizes the skin entrance dose. Suboptimal position: the patient is closer to the x-ray source; the image detector remains close to the patient. Proximity of the patient to the x-ray source increases the skin entrance dose by about 40%. Worst position: the patient remains closer to the x-ray source; the image detector is now elevated away from the patient. The combination of the patient proximity to the x-ray source and increased distance of the image detector from the patient results in a skin entrance dose that is 2.6 times the dose in the best position.

Staff should be directed to notify the physician when $K_{a,r}$ is greater than 3 Gy and then every 1 Gy thereafter. When high-dose radiation is administered, the operator must consciously balance the risk against the benefits of proceeding.

The positions of the detector and table are under the operator's control and responsibility (Figure 6.3). Fluoroscopy should only be activated when directly looking at the monitor. Cine imaging should be limited to documenting significant findings or changes in status. The operator is responsible for actively participating and managing all the parameters of radiation exposure, such as angulation, frame rate, collimation, protective shielding, and table and receptor height.

The spatial distribution of scatter radiation within the fluoroscopy laboratory is asymmetrical. Maximum scatter radiation to the angiographer occurs when standing on the x-ray tube side of the patient during the lateral or oblique view (e.g., positioned at the patient's right side when the C-arm is in the left anterior oblique [LAO] projection). Such projections that place the x-ray source close to the operator should be minimized. There is less radiation exposure at the feet than at the head.

The image detector should be positioned as close as possible to the patient's chest during radiographic imaging. When the image detector is not positioned correctly, several deleterious consequences result:

1. Patient dose increases.
2. Scatter radiation increases, resulting in higher occupational hazards.
3. Geometric magnification increases, so image blurring increases, and image quality is degraded.

The patient should be positioned as far away from the x-ray source as possible to limit the radiation dose. The source-to-skin distance can be increased by raising the table. The closer the x-ray tube is to the patient, the greater the PSD and scatter.

Angulation

Radiation exposure is highly dependent on the angle of the C-arm gantry at which the x-rays are projected. Oblique views (LAO and RAO) and steep angulations increase radiation exposure; although these may improve visualization, a view with less exposure is preferred when possible. Steep angles, especially in the LAO cranial view, should be minimized as much as possible because this angle places the x-ray tube next to the operator and increases scatter because of the depth of penetration needed (Figure 6.4).

The angiographer should limit the use of steep RAO–LAO and cranial–caudal angulation to situations when the enhanced visualization is indispensable. When the C-arm is positioned in steep angulations, the length of the x-ray path through the patient increases, augmenting scatter. An increase in PSD results for two reasons:

- 1) The source-to-skin distance is decreased.
- 2) The ADRC will increase radiation output to maintain a constant detector dose. Therefore, x-ray output rises, increasing scatter. Approximately 25% of the x-ray beam intensity is attenuated for each 1 cm of soft tissue.

Shielding

Effective shielding is the best approach, besides time and distance, to reduce radiation exposure. "Shielding" means putting material between the source of the radiation and the area to be protected. The idea behind shielding is the concept of *attenuation*, which is the loss in intensity of a beam of radiation as it traverses through barrier material. Attenuation results from a combination of absorption and scatter when x-rays interact with the shielding material.

Radiation shield protection materials can be composed of lead-lined glass, latex, or plastic. Lead is especially advantageous for blocking x-rays because of its high atomic number. Lead atoms have a relatively large number of protons and electrons; the electrons block the x-ray photons

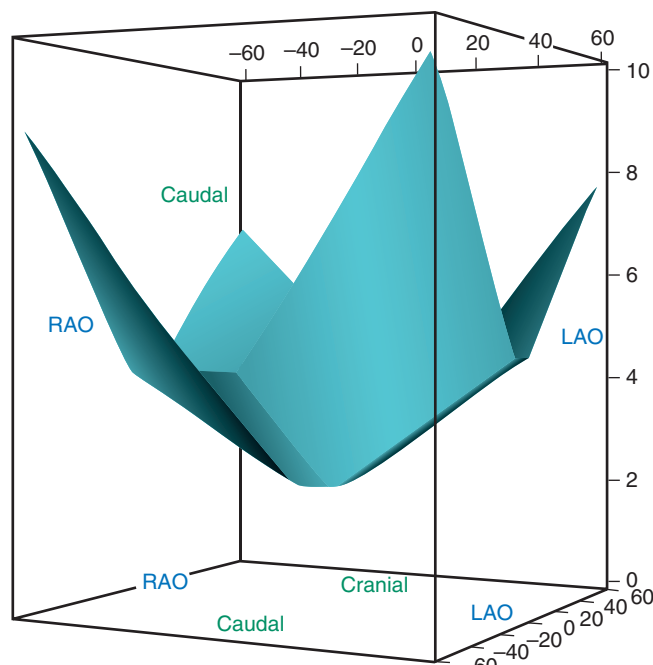


FIGURE 6.4 Air kerma rates and C-arm angulation. Three-dimensional representation of air kerma rates (mGy/sec on the ordinate) in relation to C-arm angulation during coronary angiographic acquisitions. Left anterior oblique (LAO) angulations are associated with higher air kerma rates per degree of angulation than right anterior oblique (RAO) and caudal angulations with higher air kerma rather than cranial angles.

that are transmitted by absorbing their energy and rising to a higher energy orbital. Using thicker shielding barriers can enhance the degree of protection. Layers of bismuth, antimony, and lightweight synthetic materials are usually used in garments and shields because of the heavy weight of lead.^{23–25}

Three types of shielding are commonly used in laboratories:

- Personal shielding, including leaded aprons, thyroid collars, and leaded glasses
- Leaded drapes suspended from the side of the cath table to provide protection below the table
- A ceiling-mounted shield to reduce to the operator's head, thyroid, eyes, and chest, which can diminish exposure to these areas by 95% or more

Laboratory-Based Shielding

Radiation shielding provides effective protection from scatter radiation when correctly positioned to achieve optimal protection. Unfortunately, its effectiveness may vary considerably because its use continues to be operator dependent. Current catheterization laboratory design requires the cooperation of the operator to manage the placement of the x-ray tube, the image detector, and ceiling and table-mounted shields to acquire the best images and protect catheterization laboratory personnel.^{10,23–26}

Ceiling-mounted and below-table shielding are effective and should be used routinely to provide protection from scatter. Minimizing the area of the vertical gap between the ceiling-mounted and side-rail mounted shields minimizes scatter and tube leakage through the gap. Prior generations of below-table mounted shielding limited

movement of the C-arm, but the currently available shielding is less cumbersome and provides substantial reduction in operator dose.^{25,26} Some catheterization laboratories also use overhanging lead screens to prevent radiation exposure of the brain.

The routine use of transparent ceiling-mounted shielding with a patient contour cutout protects the operator's upper body from scatter radiation. The best protection is provided when the upper body shield is located relatively far from the scatter source and close to the physician; this position minimizes the effective size of the gap between the patient and the shield. Contrary to common practice, positioning the ceiling shield closer to the source to maximize its radiation "shadow" is less effective than placing the shield closer to the operator's body. The operator should view the area of catheter insertion only through the shield, decreasing ocular exposure. When positioned correctly, shields can provide minimally 80% protection from scatter.^{20,24–26}

In-laboratory moveable barriers provide protection for staff present in the procedure room. Staff may circulate as needed but should be protected as much as possible by a moveable barrier away from the table.

Various types of ancillary shielding are available. Radiopaque pads placed on the patient have the capacity to reduce scatter radiation by 20%; care should be taken that the pads are placed outside the field of view; otherwise, scatter radiation will increase. Accessory soft shielding extensions placed along the bottom edge of the upper body shield minimizes the amount of scatter. Ancillary shielding may be especially useful in specific circumstances:

- Extremely obese patients, in whom scatter radiation is likely to be high
- Operators who frequently reach or exceed monthly radiation limits on their badges because of high volume or multiple cases requiring higher doses
- Radial artery procedures; all available types of radiation shielding should be used routinely because radial access may be associated with higher operator exposure²⁰

Personal Protection

Mandatory protective equipment includes lead aprons, thyroid collars, and leaded glasses. Although optional in some laboratories, leaded caps are strongly recommended.

Protective aprons block approximately 95% of scatter radiation. These garments are designed to protect the gonads and 80% of the blood-forming bone marrow. The standard for operators is 0.5-mm lead apron or equivalent. Catheterization laboratory staff should wear a protective apron of 0.25-mm lead equivalent or greater. The garment design is critical: those that rest weight on the shoulders are most apt to create neck and spine injuries. Those that wrap around are better, but the two-piece vest-and-kilt type is the most desirable ergonomic design.¹

Personal protective garments, eyeglasses, and head protection are necessary accessories. Radiation glasses constructed with 0.25-mm lead equivalent protection and additional side shielding are most effective. Full-gear protection includes a leaded face shield, leg protection, and protective gloves. If the latter are used, they should be

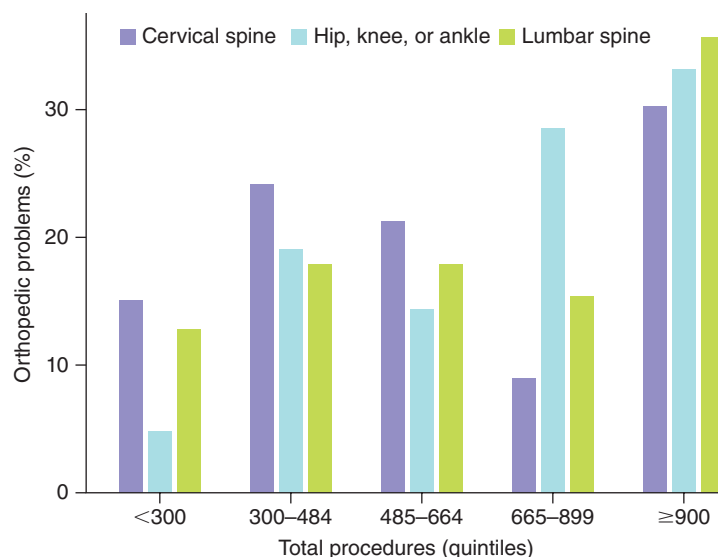


FIGURE 6.5 Frequency of orthopedic injuries in interventional cardiologists. Grouping by annual procedural volume quintile. There is a statistically significant increase in cervical, extremity, and back injuries that is case volume dependent. Annual total caseload is strongly associated with orthopedic illness ($P < .001$). (Reproduced with permission from Klein LW, Tre Y, Garratt KN, et al. Occupational health hazards of interventional cardiologists in the current decade. Results of the 2014 SCAI membership survey. *Catheter Cardiovasc Interv.* 2015;86(5):913-924.)

0.35-mm lead equivalent or greater; needle holders may eliminate the need to place one's hands in the field. All protective clothing should be examined at yearly intervals. Defective items should be withdrawn from use.^{1,2}

The COVID-19 pandemic highlighted the personal risk to catheterization laboratory personnel. Wearing an extra gown and visor in addition to radioprotective garments results in discomfort and clouding of eyewear. An enhanced emphasis on staff protection is necessary during pandemics.²⁷

OCCUPATIONAL HAZARDS OF THE CATHETERIZATION LABORATORY

Interventional physicians are exposed to the highest amounts of ionizing radiation of all medical professionals. Potential occupational hazards for cardiologists and catheterization laboratory staff have been increasingly recognized. The probability of sustaining an orthopedic injury during an interventional career is 30% to 60%; other probabilities are 3% for cancer, 8% for skin disease, 12% for hypertension and hypercholesterolemia, and 5% for cataracts. These frequencies are two to seven times higher than other medical occupations.^{6,7,28,29} Some risks are stochastic, and others are deterministic, and there is likely individual variability in susceptibility. Additionally, 7% of operators have had to limit their caseload because of excess radiation exposure, and 9% have had a health-related period of absence. Of particular note is the association between occupational radiation exposure and posterior lens opacities,³⁰ brain malignancies,³¹ and carotid atherosclerosis.³²

Orthopedic Injuries

Working in an interventional laboratory is associated with an increased incidence of orthopedic injuries, particularly to the cervical and lumbar spine. These injuries are linked

to the cumulative effects of bearing the weight of lead aprons.⁶⁻⁸ Additionally, awkward orthopedic ergonomic postures are promoted by the design of the catheterization laboratory environment; these include monitors placed out of the line of natural sight views and the continued need to turn one's head to see all the activities taking place and the control room. Consequently, interventional practice has a high incidence (40%–50%) of occupational-related orthopedic injuries,⁷ which have been shown to be age and caseload dependent (Figure 6.5). Orthopedic injuries are much more likely in those wearing lead aprons working in the fluoroscopic laboratory compared with colleagues who do not carry the weight of lead aprons. These occupational-related injuries result in missed work and surgery and for some, shortened careers. Moreover, interventional procedures have become increasingly complex and lengthy and performed at high volumes, which has increased the occurrence of these injuries.

Cardiovascular Risk

Occupational radiation exposure has been associated with hypertension, hypercholesterolemia, and precursors of atherosclerosis.²⁸ Lengthened sarcomere length and early vascular aging have been identified, suggesting that occupational exposure to radiation may increase the risk of developing these illnesses.³⁰ Although at this time there is no definitive evidence of increased risk of coronary artery disease, it is likely that future studies will establish a connection.

THE CATHETERIZATION LABORATORY OF THE FUTURE

The proper use of shielding is voluntary and remains operator dependent. In the future, radiation safety will not be predicated on the cooperation of operators; rather, the



architecture of the laboratory will ensure maximum patient and staff radiation protection.^{6,33} Designs that lessen the burden of wearing protective garments and its attendant injuries will also be advantageous. More favorable ergonomic catheterization laboratory design is also desirable.

Automated mechanism designs to place shielding correctly, and surrounding shielding shells around the patient are currently being tested. Shielding systems that surround the patient to minimize scatter are becoming commercially available. Other innovative techniques being studied include (1) ceiling- or floor-mounted personal lead to reduce orthopedic injuries resulting from heavy protective apparel without compromising radiation protection while providing ergonomic protection and complete freedom of movement; (2) robotic-controlled PCI, which has great promise in revolutionizing the procedure but will not be widely adopted until the cost of disposables is controlled; and (3) digital amplification of images in real-time display with limited radiation dose, which is being actively investigated.

REFERENCES

- Chambers CE, Fetterly KA, Holzer R, et al. Radiation safety program for the cardiac catheterization laboratory. *Catheter Cardiovasc Interv*. 2011;77:546-556.
- Christopoulos G, Makke L, Christakopoulos G, et al. Optimizing radiation safety in the cardiac catheterization laboratory: a practical approach. *Catheter Cardiovasc Interv*. 2016;87:291-301.
- Fetterly KA, Mathew V, Lennon R, Bell MR, Holmes DR Jr, Rihal CS. Radiation dose reduction in the invasive cardiovascular laboratory: implementing a culture and philosophy of radiation safety. *JACC Cardiovasc Interv*. 2012;5:866-873.
- Hirshfeld JW Jr, Balter S, Brinker JA, et al. ACCF/AHA/HRS/SCAI Clinical Competence Statement on physician knowledge to optimize patient safety and image quality in fluoroscopically guided invasive cardiovascular procedures. *Circulation*. 2005;111:511-532.
- Hirshfeld JW Jr, Ferrari VA, Bengel FM, et al. ACC/HRS/NASCI/SCAI/SCCT expert consensus document on optimal use of ionizing radiation in cardiovascular imaging: best practices for safety and effectiveness: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2018;71:e283-e351.
- Klein LW, Goldstein JA, Haines D, et al. Multispecialty Society Position Statement. Occupational hazards of the catheterization laboratory: shifting the paradigm for healthcare workers' protection. *J Am Coll Cardiol*. 2020;75:1718-1724.
- Klein LW, Tre Y, Garratt KN, et al. Occupational health hazards of interventional cardiologists in the current decade. Results of the 2014 SCAI membership survey. *Catheter Cardiovasc Interv*. 2015;86(5):913-924.
- Klein LW, Miller DL, Balter S, et al on behalf of the members of the Joint Inter-Society Task Force on Occupational Hazards in the Interventional Laboratory. Occupational hazards in the interventional laboratory. Time for a safer environment. *Radiology*. 2009;250:538-544.
- Balter S, Moses J. Managing patient dose in interventional cardiology. *Catheter Cardiovasc Interv*. 2007;70:244-249.
- Kim KP, Miller DL, Balter S, et al. Occupational radiation doses to operators performing cardiac catheterization procedures. *Health Physics*. 2008;94:211-227.
- Balter S, Hopewell JW, Miller DL, Wagner LK, Zelefsky MJ. Fluoroscopically guided interventional procedures: a review of radiation effects on patients' skin and hair. *Radiology*. 2010;254:326-341.
- Leung KC, Martin CJ. Effective doses for coronary angiography. *Br J Radiol*. 1996;69:426-431.
- Bakalyar DM, Castellani MD, Saffian RD. Radiation exposure to patients undergoing diagnostic and interventional cardiac catheterization procedures. *Cathet Cardiovasc Diagn*. 1997;42:121-125.
- Katritsis D, Elfstathopoulos E, Betson S, Korovesis S, Webb-Peploe MM. Radiation exposure of patients and coronary arteries in the stent era: a prospective study. *Cathet Cardiovasc Interv*. 2000;51:259-264.
- Daneault B, Balter S, Kodali SK, et al. Patient radiation exposure during transcatheter aortic valve replacement procedures. *EuroIntervention*. 2012;8:679-684.
- Fetterly KA, Lennon RJ, Bell MR, Holmes DR Jr, Rihal CS. Clinical determinants of radiation dose in percutaneous coronary interventional procedures: influence of patient size, procedure complexity, and performing physician. *JACC Cardiovasc Interv*. 2011;4:336-343.
- Chambers CE. Radiation dose in percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2011;4:344-346.
- Bashore T. Radiation safety in the cardiac catheterization laboratory. *Am Heart J*. 2004;147:375-378.
- Murat D, Wilken-Tergau C, Gottwald U, Nemitz O, Uher T, Schulz E. Effects of real-time dosimetry on staff radiation exposure in the cardiac catheterization laboratory. *J Invasive Cardiol*. 2021;33:E337-E341.
- Rao SV, Tremmel JA, Golchris IC, et al. Best practices for transradial angiography and intervention: a consensus statement from the Society for Cardiovascular Angiography and Intervention's Transradial Working Group. *Catheter Cardiovasc Interv*. 2014;83:228-236.
- International Commission On Radiological Protection, Pregnancy and Medical Radiation. *Annals of the ICRP* (publication 84). Pergamon Press; 2000. Available at: <https://www.icrp.org/publication.asp?id=icrp%20publication%2084>.
- National Council on Radiation Protection and Measurements. *Radiation dose management for fluoroscopically-guided interventional medical procedures* (NCRP report no. 168). National Council on Radiation Protection and Measurements; 2011. Available at: <https://app.knovel.com/kn/resources/kpRDMFGIM5/toc>.
- Stahl CM, Meisinger QC, Andre MP, Kinney TB, Newton IG. Radiation risk to the fluoroscopy operator and staff. *AJR Am J Roentgenol*. 2016;207:737-744.
- Klein LW. Proper shielding technique in protecting operators and staff from radiation exposure in the fluoroscopy environment. *J Invasive Cardiol*. 2021;33:E342-E343.
- Klein LW, Maroney J. Optimizing operator protection by proper radiation shield positioning in the interventional cardiology suite. *JACC Cardiovasc Interv*. 2011;10:1140-1141.
- Fetterly KA, Magnuson DJ, Tannahill GM, Hindal MD, Mathew V. Effective use of radiation shields to minimize operator dose during invasive cardiology procedures. *JACC Cardiovasc Interv*. 2011;10:1133-1139.
- Banning AP, Sabate M, Valgimigli M. The impact of the COVID-19 pandemic upon patients, staff, and on the future practices of percutaneous coronary intervention. *Eur Heart J Suppl*. 2020;22(suppl Pt t):P13-P18.
- Andreassi MG, Piccaluga E, Guagliumi G, Del Greco M, Gaita F, Picano E. Occupational health risks in cardiac catheterization laboratory workers. *Circ Cardiovasc Interv*. 2016;9:e003273.
- Orme NM, Rihal CS, Gulati R, et al. Occupational health hazards of working in the interventional laboratory: a multisite case control study of physicians and allied staff. *J Am Coll Cardiol*. 2015;65:820-826.
- Ciraj-Bjelac O, Rehani MM, Sim KH, Liew HB, Vano E, Kleiman NJ. Risk for radiation-induced cataract for staff in interventional cardiology: is there reason for concern? *Catheter Cardiovasc Interv*. 2010;76:826-834.
- Roguin A, Goldstein J, Bar O. Brain tumours among interventional cardiologists: a cause for alarm? Report of four new cases from two cities and a review of the literature. *EuroIntervention*. 2012;7:1081-1086.
- Andreassi MG, Piccaluga E, Gargani L, et al. Subclinical carotid atherosclerosis and early vascular aging from long-term low-dose ionizing radiation exposure: a genetic, telomere, and vascular ultrasound study in cardiac catheterization laboratory staff. *JACC Cardiovasc Interv*. 2015;8:616-627.
- Klein LW, Miller DL, Goldstein J, et al on behalf of the members of the Multispecialty Occupational Health Group. The catheterization laboratory and interventional vascular suite of the future: anticipating innovations in design and function. *Catheter Cardiovasc Interv*. 2011;77:447-455.



7 Contrast Selection

MAURO CHIARITO, USMAN BABER, GEORGE DANGAS, AND ROXANA MEHRAN

INTRODUCTION, 115

CHEMICAL STRUCTURE, 115

CLASSIFICATION, 115

PROPERTIES OF CONTRAST MEDIA, 116

Hematologic Effects, 116

Hemodynamic Effects, 117

Electrophysiologic Effects, 117

ADVERSE EFFECTS RELATED TO

CONTRAST MEDIA ADMINISTRATION, 117

ISCHEMIC COMPLICATIONS, 118

CONTRAST-ASSOCIATED ACUTE KIDNEY
INJURY, 119

Definition and Clinical Course, 119

Incidence, 119

Risk Factors, 119

Pathophysiology, 120

Controversies in Clinical Practice, 122

Preventive Strategies, 122

Prognosis, 124

CONCLUSIONS, 124

ACKNOWLEDGMENTS, 125

INTRODUCTION

Iodinated contrast media (CM) are widely used in interventional cardiology. Efficacy is predicated on the capacity to opacify intravascular structures; however, when selecting a CM, other important properties should be considered. Most notably, chemical properties such as ionicity, osmolality, and viscosity, as well as the potential for adverse effects, should be incorporated in the decision for CM selection. This chapter aims to provide a comprehensive review of various CM used in interventional cardiology in regard to their structure and properties. Special consideration is given to potential adverse effects, with evidence-based suggestions for prevention and management.

CHEMICAL STRUCTURE

Contrast media consist of an organic carrier molecule (benzene ring) with iodine located at the 2, 4, and 6 positions and organic side chains at the 1, 3, and 5 positions. They are traditionally classified based on their structure, ionicity, osmolality, and viscosity; nonetheless, these properties are strictly interconnected.

Structure refers to the number of benzene rings per molecule. Monomers consist of a single tri-iodinated benzene ring, AND dimers consist of two bound tri-iodinated benzene rings. Depending on the side chain, CM can be ionic or nonionic. Ionic CM are substituted by a carboxyl side chain (anion), which conjugates with a cation (usually sodium), resulting in a water-soluble compound. In contrast, nonionic side chains consist of hydrophilic hydroxyl groups and hence do not ionize in solution. [Figure 7.1](#) illustrates different CM according to structure and ionicity.

Osmolality refers to the number of osmotically active molecules per fluid mass. As noted earlier, ionic CM dissociate when placed in a solution and therefore are expected to have higher osmolality. The nomenclature regarding osmolality is based on normal blood osmolality (280 mOsm/kg H₂O).

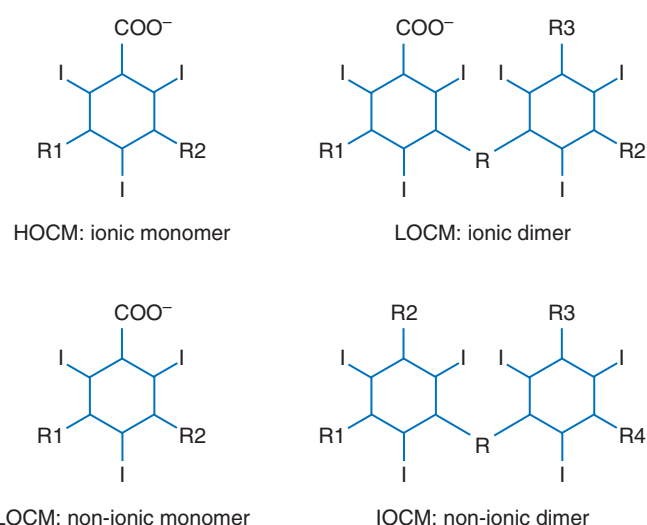


FIGURE 7.1 Prototypic structures of different classes of contrast media. *HO-CM*, High-osmolality contrast media; *IO-CM*, iso-osmolar contrast media; *LO-CM*, low-osmolality contrast media.

Viscosity represents the intrinsic resistance of a fluid to flow and is primarily determined by the other properties of the CM and is influenced by temperature. As a general rule, viscosity is directly related to particle size, is inversely related to osmolality, and decreases with warming. It is important to note that by definition, agents with lower viscosity maintain flow rates at lower injection pressures.¹

CLASSIFICATION

The first generation of CM were high-osmolality contrast media (HO-CM) with an osmolality of greater than 1400 mOsm/kg. This class is composed of ionic monomers and includes diatrizoate, metrizoate, iothalamate ([Figure 7.2](#)). The hyperosmolality of these agents contributes to significant fluid shifts, whereas ionicity and the

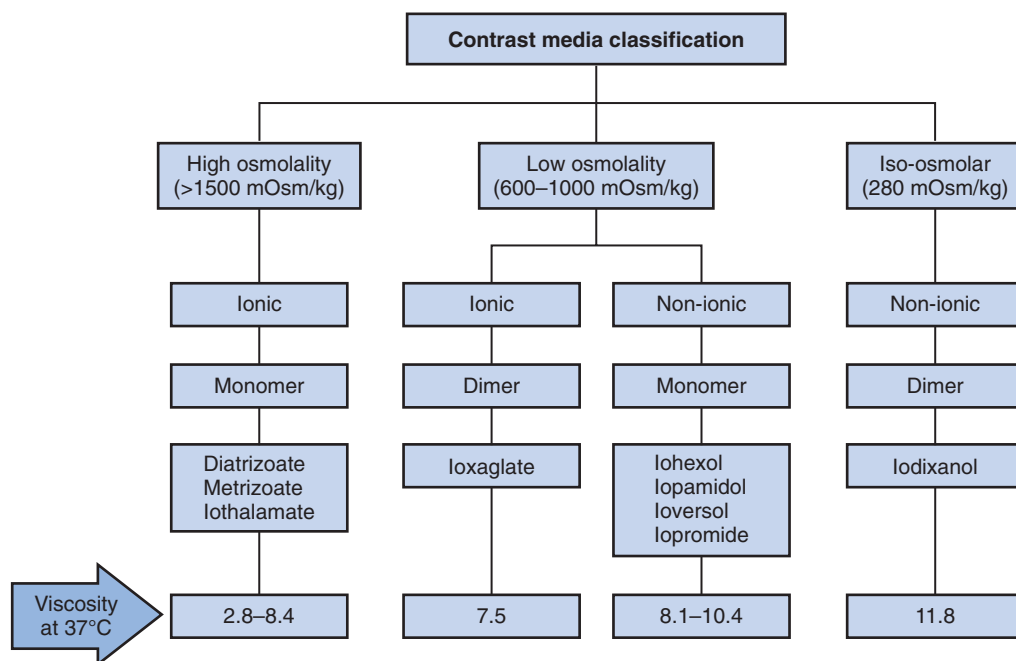


FIGURE 7.2 Contrast media classification.

additives that they contain promote cardiotoxic and arrhythmogenic effects.²

The next generation of low-osmolality contrast media (LOCM) was characterized by an osmolality between 600 and 850 mOsm/kg. First in this class was the ionic dimer ioxaglate with an osmolality of 600 mOsm/kg. Subsequently, monomeric, nonionic LOCM were developed with osmolalities varying between 500 and 850 mOsm/kg. Included in this class are some of the most used agents, such as iopamidol, iohexol, iopromide, ioxilan, ioxaglate, iobitridol, and ioversol (see Figure 7.2). Early studies showed a significantly improved safety profile of LOCM compared with HOCM in regard to arrhythmogenic potential, hemodynamic abnormalities, and contrast-induced nephropathy, resulting in a substantial decrease in HOCM use.²

The last class of agents has an osmolality similar to plasma (290 mOsm/kg) and is therefore classified as iso-osmolar contrast media (IOCM). This class only includes the nonionic dimer iodixanol, which is unique among contrast agents for its high viscosity¹ (see Figure 7.2).

PROPERTIES OF CONTRAST MEDIA

Contrast media are known to have several properties that are clinically significant in the setting of percutaneous coronary intervention (PCI). These include hematologic, hemodynamic, and electrophysiological effects.

Hematologic Effects

Several lines of evidence suggest that CM also modulate blood thrombogenicity, an effect that appears to vary in relation to the ionic potential of the different CM. The potential effects of CM on coagulation were first suspected

after observing that thrombus development is faster in angiographic catheters filled with blood when mixed with nonionic CM.³ Subsequent studies suggested that CM exert various effects on the clotting cascade, including inhibition of the intrinsic and extrinsic coagulation pathways, as well as direct or indirect platelets activation, and lower efficiency of the fibrinolytic system.^{3,4}

In vitro studies showed that the ionic LOCM ioxaglate exerts prominent anticoagulant effects by inhibiting the activation of factors V and VIII and by decreasing thrombin-induced fibrin polymerization.⁴ Further in vitro studies showed that all CM have an intrinsic anticoagulant effect; however, more prominent inhibition was noted when the ionic agent ioxaglate was compared with other nonionic media.⁴ However, the clinical significance of these observations is controversial, especially when considering that the difference in anticoagulant effect observed with the nonionic agents is equalized with the use of heparin.

Similarly, the effect of CM on platelets differs between ionic and nonionic agents. In a study evaluating the in vitro effects of different classes of CM on platelet function as measured by the release of platelet factor-4, serotonin, and platelet-derived growth factor-AB, ioxaglate had no effect on platelet function, whereas iodixanol and iohexol showed moderate and major degrees of platelet activation, respectively.

In an in vitro study, the ionic agent ioxaglate was not associated with thrombus formation, whereas the nonionic agents iohexol and iodixanol were associated with a 10-fold increase in thrombus formation compared with saline controls, and the thrombi formed were more resistant to fibrinolysis.

Importantly, platelet activation properties are limited to the vessels receiving the contrast medium and vanish when the CM is no longer being injected, as enhanced platelet deposition has been reported only on vascular surfaces exposed to ionic contrast.

Hemodynamic Effects

Contrast media are also associated with several hemodynamic effects, such as fluid shifts, peripheral vasodilation, and changes in cardiac contractility.

Most of the agents used are hyperosmolar to plasma (with the exception of iodixanol, which is iso-osmolar); therefore, rapid infusion of a large amount of CM can cause fluid shifts from the extracellular to the intravascular compartment and can lead to fluid overload and even pulmonary edema.

Additionally, CM are associated with systemic vasodilation and subsequent hypotension. Hyperosmolality is again a potential explanation for this phenomenon, but histamine release from basophils has also been proposed as a possible explanation. Hypotension can also be attributed to the direct effect of the CM to the myocardium, causing a transient decrease in cardiac contractility and a subsequent decrease in cardiac output.¹

Finally, CM may exert other cardiovascular effects, ranging from common vasovagal responses to rare ventricular arrhythmias. Within seconds after coronary injection, transient sinus bradycardia and atrioventricular conduction delay could occur, likely secondary to a vasovagal response. This type of reaction does not prohibit further injection but is reasonable to slow the rate of injection because this may mitigate the response.⁵

Electrophysiologic Effects

Changes in the cardiac cell membrane excitability can also occur, resulting in a decrease in the ventricular fibrillation threshold and predisposition to ventricular arrhythmias. The incidence of ventricular arrhythmias decreases significantly if calcium cations are added, indicating that calcium chelation by anions dissociated from ionic CM is at least partially responsible for this effect.⁶ Additionally, these types of arrhythmias are more common with the HOCM, suggesting a role of hyperosmolality in their pathogenesis.⁵

ADVERSE EFFECTS RELATED TO CONTRAST MEDIA ADMINISTRATION

Hypersensitivity reactions after CM administration are fairly common, with an incidence that varies depending on the type of CM used. Sutton et al.,⁷ in a study comparing the most used CM, reported that early reactions (within 24 hours) occurred in 22.2%, 7.6%, and 8.8% of those receiving ioxaglate, iodixanol, and iopamidol, respectively, whereas late skin reactions (>24 hours to 7 days) occurred in 12.2% of those receiving iodixanol, 4.3% of those receiving ioxaglate, and 4.2% of those receiving iopamidol.

The pathophysiology of CM reactions remains disputed. Although clinically similar to anaphylaxis, it is rarely immunoglobulin E mediated. The most possible explanation is of an anaphylactoid reaction resulting from direct activation of mast cells and basophils by CM, with a subsequent release of histamine.

Several factors have been associated with increased risk for contrast reactions. The class of CM correlates strongly with the propensity for a CM reaction. In general, HOCM are associated with a higher incidence of reactions compared with LOCM. Additionally, evidence suggests that the nonionic iso-osmolar agent iodixanol might be the safer agent to use in terms of hypersensitivity reactions.

A personal history of an anaphylactoid reaction is probably the most important risk factor for it. Moreover, any personal history of atopy doubles the risk for developing an adverse reaction to CM. Also, the use of beta-blockers has been associated with an increased risk for anaphylactoid reaction.⁸

A common misconception is that contrast allergy is related to the iodine in the CM. Indeed, the antigenic epitope is on the organic compound. Iodine is present throughout the body, and a true allergy to iodine would be incompatible with life. It also needs to be clarified that patients with shellfish allergy are not at high risk for contrast reaction because the specific antigen responsible for shellfish allergy is a shellfish-specific tropomyosin.

Clinical manifestations of hypersensitivity reactions can be broadly categorized in immediate reactions that happen within minutes to 1 hour and delayed reactions that occur within 1 hour to 1 week after.

Immediate reactions usually manifest as urticarial rash and pruritus. On rare occasions, a more dramatic picture occurs, with angioedema, laryngospasm, and bronchospasm causing stridor, wheezing, and respiratory distress. Also, circulatory collapse may occur with hypotension and tachycardia, leading to death if not promptly treated.

Delayed reactions usually occur within 2 days (although delayed reactions were described as late as 1 week after). Common manifestations include skin rash, fatigue, fever, congestion, abdominal pain, diarrhea, constipation, and polyarthropathy.⁸ A personal history of a delayed reaction is also associated with an increased risk of an immediate reaction on repeat exposure to CM.

The management of anaphylactoid reactions depends on the severity of the reaction. In mild reactions (urticarial rash, pruritus), the infusion should be stopped, intravenous (IV) antihistamine (e.g., diphenhydramine 50 mg) should be given, and the patient should be carefully observed for any signs of progression. In general, reactions that occur during or immediately after the CM administration tend to progress if not treated, but reactions occurring 5 minutes or more after administration tend to be self-limiting.⁶

The management of severe reactions is identical to that of anaphylaxis. The first step is to immediately stop the infusion of the contrast and give 0.3 to 0.5 mg of intramuscular epinephrine. Intubation should be performed if clinically indicated, and supplemental oxygen should be given. Normal saline boluses should be given as needed for hypotension. Additionally, 125 mg of methylprednisone should be given to prevent recurrent reactions, as well as 50 mg IV of diphenhydramine and 50 mg of ranitidine. If the patient is not responding to these measures, an epinephrine drip should be started at a rate of 2 to 10 µg/min and titrated according to blood pressure, and if needed, a vasopressor can be started. Patients taking beta-blockers may



be given glucagon 1 to 5 mg IV over 5 minutes followed by infusion of 5 to 15 $\mu\text{g}/\text{min}$.⁸ Table 7.1 summarizes the treatment of patients with hypersensitivity reactions.

Another important consideration is related to prevention measures in patients with history of hypersensitivity reaction to CM. Multiple protocols have been proposed, but a validated protocol includes 50 mg of prednisone orally at 13, 7, and 1 hour before the procedure in combination with 50 mg of IV diphenhydramine 1 hour before the procedure. For emergency procedures, LOCM or IOCM should be preferred to HOCM, and hydrocortisone 200 mg IV and diphenhydramine 50 mg IV are recommended. Note that premedication in patients with no history of adverse reaction is not recommended.⁸ Table 7.2 summarizes the recommended premedication protocols.

ISCHEMIC COMPLICATIONS

As mentioned previously in this chapter, *in vitro* studies illustrated that CM exert multiple effects on the clotting cascade, platelets, and fibrinolysis. Furthermore, early observations suggested that nonionic CM may promote clot formation in excess compared with ionic CM.⁴ Following this observation, multiple trials were conducted to evaluate the effect of the different CM classes on clot formation. Because HOCM are rarely if ever used in the modern era, we focus on trials that only included ionic or nonionic LOCM and IOCM.

In the 1990s, several trials were conducted comparing the ionic LOCM ioxaglate with other nonionic LOCM among patients undergoing PCI.⁹⁻¹² In all of these trials, thrombotic

events and subacute recoil were more common among patients receiving nonionic CM. Of note, these studies were performed in the prestent era or before the advent of glycoprotein (GP) IIb/IIIa or strong P₂Y₁₂ inhibitors.

Schröder et al.¹⁰ were the first to compare the thrombogenic potential of ionic versus nonionic CM in the stent era in a randomized controlled trial of 2000 patients.¹⁰ In this study, the incidence of reocclusion necessitating repeat angioplasty occurred in 2.9% of the patients receiving the nonionic iomeprol versus 3.0% of the patients receiving the ionic ioxaglate. Moreover, there were no significant differences in the rate of major ischemic complications between iomeprol and ioxaglate (emergency bypass surgery, 0.8% vs 0.7%; myocardial infarction [MI], 1.8 vs 2.0%; cardiac death during hospital stay, 0.2% vs 0.2%, respectively).

Studies comparing the nonionic IOCM iodixanol with ionic LOCM ioxaglate have been controversial. The multicenter VIP trial (Visipaque in Percutaneous transluminal coronary angioplasty [PTCA]) compared iodixanol with ioxaglate in 1411 patients undergoing coronary intervention.¹¹ In the 2-day period after PCI, major adverse cardiac events (a composite of death, stroke, MI, coronary artery bypass grafting, and revascularization) were comparable between groups (4.7% vs 3.9% for iodixanol vs ioxaglate, respectively). Similarly, at 1-month follow-up, no significant difference was noted between the groups in the rates of rehospitalization secondary to major adverse cardiovascular events (MACEs).

In contrast to the VIP trial, the COURT trial (randomized trial of CM use in high-risk PTCA), showed improved ischemic outcomes with iodixanol compared with ioxaglate.¹²

TABLE 7.1 Presentation and Treatment of Hypersensitivity Reactions

SEVERITY	SYMPTOMS	MANAGEMENT
Mild	Urticarial rash Pruritus	Stop infusion Diphenhydramine 50 mg IV Observe for progression to severe
Severe	Hives Angioedema Laryngospasm causing stridor Bronchospasm with wheezing Respiratory distress Circulatory collapse (hypotension and tachycardia)	Stop CM infusion IM epinephrine 0.3–0.5 mg Intubation if clinically indicated Supplemental oxygen (≥ 8 –10 L) Normal saline boluses for hypotension Methylprednisone 125 mg IV Diphenhydramine 50 mg IV Ranitidine 50 mg IV
Refractory symptoms	Patients with inadequate response to IM epinephrine and IV saline	Epinephrine continuous infusion, 2–10 $\mu\text{g}/\text{min}$ Additional pressor if needed If patient taking beta-blockers and not responding to epinephrine: glucagon 1–5 mg IV over 5 min

CM, Contrast media; IM, intramuscular; IV, intravenous.

TABLE 7.2 Prevention from Contrast Media Reactions

PATIENT STATUS	RECOMMENDED PROTOCOL
No previous history of CM reaction	Premedication is not recommended
Previous history of adverse reaction (elective procedure)	Prednisone 50 mg PO 13 h, 7 h, and 1 h before procedure Diphenhydramine 50 mg PO 1 h before procedure
Previous history of adverse reaction (emergent procedure)	Hydrocortisone 200 mg IV once Diphenhydramine 50 mg IV

CM, Contrast media; IV, intravenous; PO, oral.

More specifically, the incidence of in-hospital MACEs was decreased in those receiving iodixanol compared with those receiving ioxaglate (5.4% vs 9.5%, respectively). However, this difference was attenuated and no longer significant at 30 days (9.1% vs 13.2% for iodixanol vs ioxaglate, respectively). Additionally, in the subgroup of patients treated with GP IIb/IIIa inhibitors, the in-hospital difference in MACE rates was no longer present.

Subsequently, Le Feuvre et al.¹³ compared ioxaglate and iodixanol in a single-center prospective study, which included 498 consecutive patients. More contemporary techniques were used, including clopidogrel, enoxaparin, GP IIb/IIIa inhibitors, and drug-eluting stents (DESs). In contrast to previous reports, results were in favor of ioxaglate, with the in-hospital MACE rate shown to be remarkably lower in the ioxaglate group compared with the iodixanol group (0.3% vs 4.8%, respectively).

In summary, whether differences exist in the thrombotic potential of the various classes of CM remains controversial. It appears that in the pre-DES era, the ionic LOCM ioxaglate was associated with decreased ischemic complications compared with nonionic LOCM. However, these differences have been completely attenuated in the modern era with the use of more potent antiplatelet and anticoagulant medications.

CONTRAST-ASSOCIATED ACUTE KIDNEY INJURY

The initial descriptions of patients with acute kidney injury (AKI) after IV pyelography with contrast agents dates back to the 1950s. Since then, remarkable advancements have been achieved in the knowledge of the relationship between CM and renal function and injury, as well as in the prevention of adverse events after intravascular CM administration. Nonetheless, this subject is still characterized by several uncertainties. Indeed, there is still no conclusive evidence that any preventive measure actually reduces the risk of contrast-associated acute kidney injury (CA-AKI). In addition, AKI has been noted after noncontrast procedures, too. Last, CA-AKI has not been causally linked with subsequent death thus far.¹⁴

Definition and Clinical Course

Contrast media-associated acute kidney injury frequently complicates the use of radiographic CM and constitutes the third leading cause of hospital-acquired AKI.

Historically, this decline in renal function was commonly referred to as *contrast-induced nephropathy*. However, a number of other factors, such as nephrotoxic medications, prolonged hypotension, or atheroembolism, can precipitate AKI after intravascular contrast medium administration, especially in the case of cardiac catheterization. Hence, the term *contrast-associated acute kidney injury* has gradually gained favor and replaced the term contrast-induced nephropathy.

Contrast-associated acute kidney injury is defined as the deterioration of renal function after the administration of contrast agents in the absence of other causes. Its

typical course includes an elevation of serum creatinine within 24 to 48 hours of contrast administration and a peak within 3 to 5 days, with a gradual resolution within 1 to 2 weeks after exposure. Permanent renal impairment is rare and occurs only in a minority of cases.¹⁵

The exact definition of CA-AKI varies within the literature, and it was historically defined as an absolute rise in serum creatinine of greater than 0.5 mg/dL or a 25% increase from baseline within 48 hours from contrast administration.^{14,15}

However, this definition resulted to be poorly specific. Currently, the definition proposed by the Kidney Disease Improving Global Outcomes (KDIGO) working group is the most used and is based on an increase in plasma creatinine level by a factor of 1.5 times or more over the baseline value within 7 days after contrast medium administration or by at least 0.3 mg/dL over the baseline value within 48 hours after exposure to contrast medium or a urinary volume of less than 0.5 mL/kg/h lasting for at least 6 hours after exposure.¹⁵ Of note, a CA-AKI diagnosis is not based on a marker of injury (e.g., troponin to define myocardial injury or MI) but on a marker of renal function. Indeed, plasma creatinine values are determined by the interplay of creatinine production, renal function, and the kinetics of creatinine distribution among the body's fluid compartments, resulting in poorly specificity of the increase in plasma creatinine values to define kidney injury. Last, plasma creatinine variation is insensitive in patients with normal glomerular filtration and in case of acute variation in renal function.¹⁴

Incidence

The incidence of CA-AKI varies within studies, depending on the definition used and the characteristics of the population studied. In retrospective analyses of an unselected patients undergoing PCI, CA-AKI (defined as a rise in creatinine of 0.3 or 0.5 mg/dL) was reported to range between 3% and 7%.

Of note, the presence of underlying chronic kidney disease (CKD) and other risk factors can raise the incidence of CA-AKI to as high as 50%.^{14,16}

Risk Factors

Predisposing conditions to CA-AKI can be broadly categorized to patient-related conditions and to the ones related to extrinsic factors. The most important patient-related risk factor is preexisting renal insufficiency.^{18,19}

In a study from the National Cardiovascular Data Registry Cath-Percutaneous Coronary intervention (NCDR Cath-PCI) registry, the risk of CA-AKI and need for renal replacement therapy in patients with normal baseline renal function was 5.2% and 0.1%, but it reached 26.6% and 4.3%, respectively, in patients with severe CKD at baseline (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²). Moreover, this risk was further enhanced among patients with additional risk factors, such as PCI performed in the setting of ST-segment elevation myocardial infarction (STEMI): a number of studies reported that patients with severe CKD at baseline presenting with STEMI represented the highest risk subgroup,



reporting CA-AKI in up to 37% and need for renal replacement therapy in up to 7% of patients.^{16,17}

Similarly, the detrimental effects of CKD in the incidence of CA-AKI become even more prominent when the underlying reason for CKD is diabetes.¹⁹ Indeed, diabetes mellitus is commonly cited as one of the strongest predictors of CA-AKI, but different studies did not find it to be an independent risk factor for CA-AKI. Rather, it amplified susceptibility in patients with underlying CKD.¹⁶

Older age has also been shown to be an independent predictor of CA-AKI.^{19,20} Possible explanations for this observation could be the gradual loss of nephrons and decline of renal function that naturally happen with aging as well as the multiple comorbidities that are found in the older adult population.

Any condition associated with inadequate renal perfusion can be a major risk factor. Specifically, the presence of heart failure, hypovolemia, and hemodynamic instability and the need for mechanical circulatory support have been shown to increase the incidence of CA-AKI.

The presence of anemia is an additional well-described but underappreciated risk factor. In a study of 6773 patients treated with PCI, Nikolsky et al.²⁰ showed an inverse association between the incidence of CA-AKI and baseline hematocrit. The presence of multiple comorbidities in the anemic patients partially explains this association, and hypoxic renal injury may offer an additional explanation.

Procedure-related factors such as the type and volume of CM used can also influence the incidence of CA-AKI. The importance of contrast volume was first shown by McCullough et al.²¹ in a cohort of 1826 consecutive patients undergoing coronary intervention. In this study, increasing contrast volume was a major risk factor for CA-AKI, and the risk of CA-AKI was minimal in patients receiving less than 100 mL of CM. Subsequently, Freeman et al.²² developed a formula for calculating the maximum radiographic contrast dose (MRCD) allowed to avoid nephropathy requiring dialysis. According to this study, $MRCD = 5 \text{ mL} \times \text{body weight (kg)} / \text{serum creatinine (mg/dL)}$, and the authors demonstrated that after multivariable adjustment, overpassing the MRCD was the strongest independent predictor for dialysis.

A further study performed by Gurm et al.²⁴ showed that the risk of CA-AKI and in-hospital dialysis was directly associated with increasing contrast volume adjusted for renal function. Furthermore, this risk was significantly increased when the ratio of contrast dose and eGFR exceeded 2 and was dramatically elevated in patients with ratio higher than 3.

The type of CM used also influences the risk for CA-AKI. Multiple studies in the 1990s showed that in patients with underlying renal impairment, the use of HOCM is associated with a higher incidence of CA-AKI when compared with LOCM. Studies comparing the nonionic IOCM iodixanol with various LOCM have had various results. In general, it appears to be a benefit of the IOCM iodixanol over the ionic LOCM ioxaglate and the nonionic LOCM iohexol. However, when comparing iodixanol to the nonionic LOCM, iopamidol, or ioversol, no significant differences were observed.²⁵

To assess the cumulative risk of the aforementioned risk factors, Mehran et al.²⁰ developed in 2004 a first simple risk score for predicting CA-AKI after PCI using easily available information. In 2012, Gurm et al.,²⁶ using data from 68,573 PCI performed in Michigan, developed a computational tool for predicting the risk of CA-AKI. The calculator for this model can be found at <https://bmc2.org/calculators/cin>. In light of the relevant progresses achieved in the field of PCI in the past 20 years, coupled with the improvement in risk assessment and preventive measures for CA-AKI (e.g., judicious use of low- or iso-osmolality contrast agents, intravascular volume expansion,^{27,28} and periprocedural interruption of nephrotoxic medications), Mehran et al.¹⁹ recently developed and internally validated an updated risk score for CA-AKI prediction (Figure 7.3), which differs from the previous version mainly with respect to the inclusion of patients presenting with STEMI or cardiogenic shock. The updated Mehran risk score includes only eight readily available clinical variables, and the inclusion of procedural features only slightly increased the accuracy of the risk score. Of note, the authors reported a significant association between CA-AKI and mortality, mainly because of excess 30-day mortality.¹⁹

Pathophysiology

The exact mechanisms leading to the development of CA-AKI remain unclear. These mechanisms include the potential interplay of cytotoxic effects of CM, auto- and paracrine factors, and altered rheologic properties that affect renal hemodynamics and tubulodynamics, resulting in regional hypoxia.²⁹ Taken singularly, these modest changes are unlikely to account for the substantial changes in renal function that are often noticed with CA-AKI.

The mechanisms leading to CA-AKI may be classified as direct and indirect.^{29,30} Direct effects are related to the biochemical properties of the specific CM. After nephron exposure to CM, the first marker of tubular epithelial injury is represented by the redistribution of Na^+/K^+ -ATPase from the basolateral to the luminal surface of the tubular epithelium, resulting in loss of cell polarity, and in turn in altered ion transport across the cells and increased sodium delivery to the macula densa and renal vasoconstriction through tubuloglomerular feedback. Based on the degree and progression of cellular injury, the detachment of epithelial cells from the basement membranes causes luminal obstruction, increased intratubular pressure, and reduction in the GFR. Further direct toxic effects are mediated via induction of cellular energy failure and disruption of calcium homeostasis, ultimately leading to apoptosis.^{29,30}

Conversely, the indirect effects of CM are related to systemic or regional decrease in renal perfusion. Based on normal physiology, the outer medulla is more susceptible to hypoxia and is likely differentially affected by CM administration and decreased perfusion. More specifically, CM have been associated with systemic hemodynamic imbalances and alteration of the fine balance between local vasodilators (nitric oxide [NO], prostaglandin E₂, dopamine) and vasoconstrictors (angiotensin II, endothelin, adenosine) in the renal medulla, resulting in varying degrees of hypoxia.^{29,30}

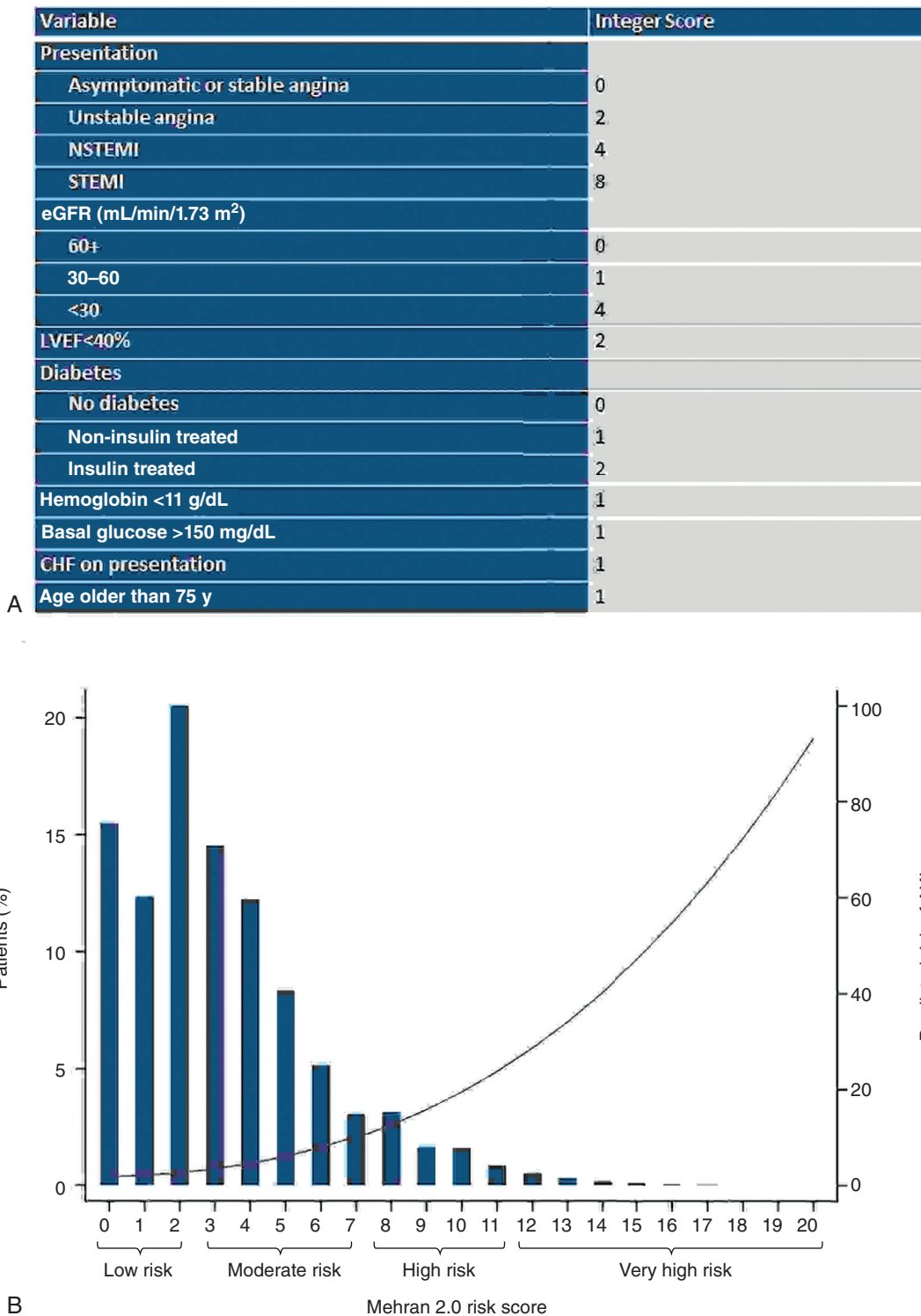


FIGURE 7.3 Algorithm for contrast-associated acute kidney injury risk assessment according to the Mehran 2.0 risk score. *AKI*, Acute kidney injury; *CHF*, congestive heart failure class III to IV by the New York Heart Association or history of pulmonary edema; *eGFR*, estimated glomerular filtration rate; *LVEF*, left ventricular ejection fraction; *NSTEMI*, non-ST-elevation myocardial infarction; *STEMI*, ST-elevation myocardial infarction.

The intrarenal vasoconstriction is induced by CM through the release of vasoactive substances, resulting in reduced glomerular blood flow and reduced oxygen delivery to the metabolically active parts of the nephron. In addition, contrast agents increase blood viscosity, leading to further reduction of the microcirculatory flow and to changes in blood osmolality, which in turn impair the

plasticity of erythrocytes and may increase the risk of microvascular thrombosis.

Additionally, CM administration appears to increase the formation of reactive oxygen species. High oxidative stress may further decrease the formation of NO, thereby promoting vasoconstriction. Moreover, the anatomy of the vasculature in the renal medulla may offer an additional explanation.

The vasa recta that supply the renal medulla are long, narrow, low-caliber vessels, so further reduction in medullary blood flow may occur because of changes in viscosity, especially when the high-viscosity IOCM are used.³⁰

Controversies in Clinical Practice

In the past decades, several studies have questioned the relevance of CA-AKI in current clinical practice. This uncertainty is largely related to the fact that increases in serum creatinine consistent with those required to be classified as CA-AKI have been reported in patients not receiving contrast agents and that such increases are common among hospitalized patients in general.^{31,32} Moreover, serum creatinine is directly and indirectly influenced by a broad range of factors.¹⁵

Many studies compared the incidence of CA-AKI among patients receiving or not IV CM. The evidence on this subject has been summarized by two meta-analyses of observational studies, which showed no difference in the risk of CA-AKI among patients receiving or not IV CM^{31,32} or even a lower risk of CA-AKI in patients receiving IV CM. Of note, most of the included studies suffered from selection or indication bias because frail patients at high risk for impairment of renal function are less likely to be exposed to contrast agents.³² Nonetheless, the adverse prognosis associated with the occurrence of CA-AKI justifies intensified surveillance in high-risk patients aimed at limiting the risk of renal function impairment after CM administration.¹⁹

Preventive Strategies

Periprocedural Hydration

Prophylactic volume expansion with intravenous fluids (IVFs) is the only measure widely accepted for CA-AKI prevention to date despite limited evidence from randomized studies in its favor.

The rationale behind the use of IVFs is mainly based on the reduction in hypotensive episodes than on the dilution of CM. The first to show the beneficial effects of hydration was Solomon et al.³³ in a prospective study of 78 patients randomized to receive 0.45% saline versus a combination of 0.45% saline plus mannitol or furosemide. In this study, simple hydration provided better protection against CA-AKI than hydration plus mannitol or furosemide (10.7% vs 28.0% vs 40.0%, respectively).

Subsequent studies proved the superiority of isotonic saline over half normal saline in preventing CA-AKI, especially among high-risk patients, such as patients with diabetes and those receiving more than 250 mL of CM, whereas studies comparing different modes of fluid administration (IV vs oral) have been controversial,^{34,35} and the KDIGO guidelines recommend not using oral fluids alone in patients at increased risk of CA-AKI.¹⁵

Limited evidence is also available regarding the optimal amount of fluids as well as the duration of the hydration protocol. Overall, for hospitalized patients, the KDIGO guidelines recommend 1 mL/kg/h of IV 0.9% saline, initiated 3 to 12 hours before and 6 to 12 hours after the procedure, with the aim of achieving a urine flow rate of at least 150 mL/h because this urine output in the 6 hours after the procedure has been associated with reduced rates of AKI.¹⁵

The preprocedure assessment of central venous pressure or left ventricular end-diastolic pressure guided hydration and a tailored hydration approach was instead found to reduce the risk of CA-AKI and of adverse events associated with IV saline infusion (e.g., pulmonary edema, electrolyte imbalance, and arrhythmia).³⁶⁻³⁸

Isotonic Sodium Bicarbonate

Administration of sodium bicarbonate can cause alkalization of the urine and thus decrease free radical formation and possibly ameliorate the risk for CA-AKI. On this theoretical basis, various studies evaluated an alternative hydration protocol with sodium bicarbonate, but results have been controversial until recently.

A number of randomized trials conducted in the early 2000s provided conflicting results regarding the comparison of a hydration protocol with sodium bicarbonate and alternative saline hydration. In 2009, Brar et al.³⁶ reported a meta-analysis (for consistency throughout chapters) regarding the role of sodium bicarbonate versus normal saline administration for CA-AKI prevention, which included 3 large trials and 12 small trials. The subgroup analysis including the 3 large trials illustrated no significant benefit from sodium bicarbonate (relative risk, 0.85; 95% confidence interval [CI], 0.63–1.16), whereas pooled results from the 12 small trials with lower methodologic quality showed evidence of benefit with sodium bicarbonate. The Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial is the largest randomized trial on this subject to date: 5177 patients with stable kidney function with eGFR of 15 to 44.9 mL/min/1.73 m² or 45 to 59.9 mL/min/1.73 m² but concomitantly affected by diabetes mellitus were randomized with a two-by-two factorial design to receive 1.26% sodium bicarbonate or 0.9% saline and either oral acetylcysteine (1200 mg 1 hour before and 1 hour after angiography and then twice daily for 4 days) or matched placebo capsules. The study was prematurely interrupted after a prespecified interim analysis, showing no benefit of IV sodium bicarbonate over IV sodium chloride for the prevention of CA-AKI.³⁷ Hence, both saline and bicarbonate can be considered for the prevention of CA-AKI, but guidelines recommend saline over bicarbonate in light of the lack of any additional benefit and the higher cost of bicarbonate.^{15,38}

RenalGuard System

As mentioned earlier, hydration with normal saline has been shown to be beneficial in the prevention of CA-AKI. However, concerns surrounding excessive hydration have led investigators toward alternative strategies, which included the concomitant use of fluids with diuretics. Theoretically, apart from protecting from overhydration, the increased urine flow promotes contrast dilution with subsequent decrease in the direct toxicity on tubular cells. However, early studies testing this hypothesis have been disappointing, possibly as a result of overdiuresis and acute electrolytes imbalance.

More recently, the RenalGuard System was developed to achieve balanced hydration and diuresis via a computerized infusion system that balances the fluid administration rate with real-time diuresis. The safety and performance of the RenalGuard System were first shown in a phase II

feasibility study by Dorval et al.³⁹ Subsequently, the Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II) investigators tested this system in 194 patients with severe CKD undergoing PCI. CA-AKI (defined as an increase in creatinine ≥ 0.3 mg/dL) occurred in 16 of 146 patients in the RenalGuard group compared with 30 of 146 patients in the control group (odds ratio, 0.47; 95% CI, 0.24–0.92).⁴⁰ Consistent results were reported later by Marenzi et al.⁴¹ in the MYTHOS (Induced Diuresis with Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial. Last, the REMEDIAL III trial, which randomized 708 patients at high risk for CA-AKI scheduled for coronary and peripheral procedures to left ventricular end-diastolic pressure (LVEDP)- or RenalGuard-guided hydration, showed that RenalGuard-guided hydration was superior to LVEDP-guided hydration to prevent the composite of CA-AKI and pulmonary edema.²⁷

Removal of Contrast Media by Extracorporeal Therapies

Because CM are primarily removed from the body via the kidneys, it was reasonable to assume that different modes of extracorporeal therapies may protect from CA-AKI. However, hemodialysis performed immediately after CM administration failed to protect from CA-AKI in patients with preexisting renal impairment despite effective elimination of the CM. Similarly, despite a randomized controlled study including 114 patients showed that periprocedural continuous venovenous hemofiltration (CVVH) was protective from CA-AKI in patients with CKD undergoing PCI, this result was not confirmed by subsequent meta-analysis. In addition, the cost-effectiveness of this method raises concerns, further limiting the use of CVVH in this context.⁴²

Renal Artery Vasodilation

Fenoldopam is a selective D-1 receptor agonist, so theoretically, it could ameliorate the CM effects to the kidney via induction of renal artery vasodilation. However, in the CONTRAST (Fenoldopam Mesylate for the Prevention of Contrast-Induced Nephropathy) trial, the systemic infusion of fenoldopam in addition to hydration failed to decrease the incidence of CA-AKI.⁴³ Subsequently, selective intrarenal fenoldopam using a dedicated catheter infusion system was tested in a pilot study, showing promising results in increasing renal plasma flow with less systemic hypotension. Notably, a randomized controlled study comparing intrarenal fenoldopam with a placebo is lacking.

Theophylline is an adenosine receptor antagonist that can cause local renal vasodilation and thus ameliorate the effects of CM to the kidney. However, results from randomized trials testing the efficacy of theophylline in reducing the incidence of CA-AKI have been controversial.⁴⁴

Antioxidant Therapy

Because oxidative kidney injury is implicated in the pathophysiology of CA-AKI, antioxidants such as *N*-acetylcysteine (NAC) and ascorbic acid have been tested for CA-AKI prevention.

Early trials evaluating the use of NAC in CA-AKI prevention showed promising results, but subsequent studies

and comprehensive meta-analyses accounting for the heterogeneity in the included studies showed conflicting results. In addition, in the largest randomized controlled studies to date, the aforementioned PRESERVE trial, the use of oral NAC was ineffective in preventing CA-AKI in high-risk patients.³⁷ The study, prematurely stopped for futility by the sponsor after a prespecified interim analysis, showed no apparent benefit of NAC in terms of the primary composite endpoint of death, need for dialysis, or persistent increase of at least 50% from baseline in the serum creatinine level at 90 days.

The use of ascorbic acid for CA-AKI prevention was evaluated by Briguori et al. in a cohort of 326 patients with CKD undergoing angiography. In this study, the addition of ascorbic acid in a preventive strategy that included hydration with normal saline and NAC provided no additional protection from CA-AKI, a finding confirmed by a subsequent meta-analysis.⁴⁶

Statins

Results from several observational studies suggested a beneficial role of statins in preventing CA-AKI possibly via their antioxidant and antiinflammatory effects. However, subsequent randomized studies provided controversial findings. A meta-analysis that included eight clinical trials with a total of 1423 patients showed that short-term high-dose statin treatment can decrease the occurrence of CA-AKI compared with conventional-dose statin or placebo.⁴⁷

Since the aforementioned meta-analysis, two additional randomized trials have been conducted. Han et al.⁴⁸ randomized 2998 patients with type 2 diabetes and concomitant CKD who were undergoing angiography to rosuvastatin for 2 days before and 3 days after the procedure or no statin. Prophylactic hydration was given at the discretion of the treating physician. In this study, the incidence of CA-AKI was significantly lower among patients in the rosuvastatin group compared with control participants (2.3% vs 3.9%). Similarly, Leoncini et al.⁴⁹ studied the effect of rosuvastatin in the incidence of CA-AKI in non-ST-elevation acute coronary syndromes (ACSs). Patients were randomly assigned to receive rosuvastatin or no statin in addition to hydration and NAC. The incidence of CA-AKI was significantly lower among patients treated with rosuvastatin compared with the control group (6.7% vs 15.1%).

An updated meta-analysis including these two randomized studies showed that statins administered with NAC and normal saline reduced the risk of CA-AKI compared with NAC and normal saline alone.⁴⁶ Overall, it appears that statins may play a role in CA-AKI prevention, but further studies are needed to clarify their role in different patient subgroups (most notably CKD patients) and to compare the effect of different statin regimens.

Radial Access

Different lines of evidence reported that radial access is associated with a lower risk of CA-AKI after PCI, especially in the setting of ACS. The protective effect of radial access has been mainly ascribed to the reduced



risk of bleeding as compared with femoral access. The intricate interplay between bleeding, AKI, and subsequent death has been commonly explained by hypotension and poor kidney perfusion induced by bleeding events, further aggravated by CM administration that reach higher blood concentrations in case of lower blood volume. The MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) trial, which allocated more than 8000 patients with ACS scheduled for PCI to radial or femoral access, demonstrated that radial access was associated with a reduced risk of AKI.⁵⁰ Of note, a post-hoc analysis of this trial, which applied multistate and competing risk models to explain the mechanisms of the mortality benefit provided by radial access in the study, showed that the reduced risk of AKI in the radial access group was the main explanation for the mortality benefit, but the reduction of major bleeding had only a limited impact on subsequent mortality. Alternative mechanisms for the AKI and mortality benefit includes the lower risk of atheroembolic renal disease caused by cholesterol emboli with radial compared with femoral access.⁵¹ This compelling body of evidence resulted in strong recommendation by current guidelines in favor of radial over femoral access in patients undergoing PCI.^{38,52}

The different preventive strategies for CA-AKI and our recommendations for their use are summarized in Table 7.3.

Prognosis

Typically, CA-AKI is a self-limited condition and only rarely progresses to end-stage renal disease requiring dialysis because it usually regresses in 5 to 10 days. However, multiple observational studies illustrate that the development of CA-AKI is associated with increased length of hospital stay, adverse cardiovascular outcomes, and higher mortality rate, especially in the early phase after the occurrence of CA-AKI.

A systematic review and meta-analysis, which included 34 studies, provided further input in the deleterious effects

of CA-AKI.⁵³ With respect to mortality rate, 11 studies that did not adjust for confounding features illustrated that CA-AKI was associated with an eightfold increase in the risk of death. Importantly, this association remained significant, although relatively reduced, after adjusting for potential confounders.

The risk for adverse cardiovascular events was increased in patients with CA-AKI in all 14 studies (70,031 participants) reporting on cardiovascular events. Specifically, RR from these studies was 2.42 (95% CI; 1.62–3.64), and there was not significantly heterogeneity between studies adjusting or not adjusting for confounders.

Finally, 10 studies with a total of 19,674 participants reported an additional unadjusted mean hospitalization length that ranged from 0.5 to 8.3 days in patients with CA-AKI, with significant heterogeneity in the size of this difference. Only one study adjusted for baseline clinical characteristics, reporting 1.6 additional days of hospitalization attributable to CA-AKI.⁵³

Overall, CA-AKI has been associated with increased morbidity and mortality rates as well as prolonged hospital stays. However, it remains unclear whether the association between CA-AKI and adverse events is causal or just identifying a subgroup of very high-risk patients.

CONCLUSIONS

Iodinated CM are usually classified based on their osmolality into HOCM, LOCM, and IOCM and further categorized into ionic and nonionic. HOCM have fallen out of favor secondary to overall increased potential for adverse reactions. Ionic CM are more likely to be associated with hypersensitivity reactions, whereas some evidence postulates that IOCM might be the safer class in terms of hypersensitivity reactions. In the current era, with the use of potent antiplatelet and anticoagulant medications, the rate of thrombotic complications is similar within the different classes of CM. CA-AKI is the most common adverse reaction associated with the use of CM, especially in

TABLE 7.3 Preventive Strategies for Contrast-Associated Acute Kidney Injury

PREVENTIVE STRATEGY	RECOMMENDATION
Hydration with normal saline	Strongly recommended for all patients
Hydration with sodium bicarbonate	No additional benefit over normal saline
RenalGuard system	Investigational device; not available for commercial use
Minimize amount of CM	Strongly recommended for all patients
Use of nonionic LOCM or IOCM	Recommended for all patients, especially if renal impairment is present
Hemodialysis	Not recommended
Continuous venovenous hemofiltration	Likely beneficial but not cost-effective
Systemic fenoldopam	Not recommended
Intrarenal fenoldopam	Further studies are required to establish effectiveness
Theophylline	Controversial; currently not recommended
N-Acetylcysteine	No proven benefit Because it is safe and inexpensive, we do not recommend against its use
Ascorbic acid	Not recommended
Statins	Likely beneficial; further studies are required

CM, Contrast media; IOCM, iso-osmolar contrast media; LOCM, low-osmolality contrast media.

patients with underlying risk factors, and it has been shown to be adversely associated with increased morbidity and mortality, although it is still unclear whether this relationship is causal or only coincidental. Evidence-based approaches to prevent CA-AKI are periprocedural hydration with normal saline, use of nonionic LOCM or IOCM, and minimization of the amount of CM used.

ACKNOWLEDGMENTS

We thank Dr. Georgios Christodoulidis for his work on the first version of this chapter.

REFERENCES

- Voeltz MD, Nelson MA, McDaniel MC, Manoukian SV. The important properties of contrast media: focus on viscosity. *J Invasive Cardiol*. 2007;19:1-9.
- Piao ZE, Murdock DK, Hwang MH, Raymond RM, Scanlon PJ. Hemodynamic abnormalities during coronary angiography: comparison of Hypaque-76, Hexabrix, and Omnipaque-350. *Cathet Cardiovasc Diagn*. 1989;16:149-154.
- Al Dieri R, Béguin S, Hemker HC. The ionic contrast medium ioxaglate interferes with thrombin-mediated feedback activation of factor V, factor VIII and platelets. *J Thromb Haemost*. 2003;1:269-274.
- Jones CI, Goodall AH. Differential effects of the iodinated contrast agents ioxaglate, iohexol and iodixanol on thrombus formation and fibrinolysis. *Thromb Res*. 2003;112:65-71.
- Kyriakidis M, Jackson G, Jewitt D. Contrast media during coronary arteriography: electrocardiographic changes in the presence of normal coronary arteries. *Br J Radiol*. 1978;51:799-801.
- Thomson KR, Violante MR, Kenyon T, Fischer HW. Reduction in ventricular fibrillation using calcium-enriched Renografin 76. *Invest Radiol*. 1978;13:238-240.
- Sutton AG, Finn P, Grech ED, et al. Early and late reactions after the use of iopamidol 340, ioxaglate 320, and iodixanol 320 in cardiac catheterization. *Am Heart J*. 2001;141:677-683.
- Goss JE, Chambers CE, Heupler FA. Systemic anaphylactoid reactions to iodinated contrast media during cardiac catheterization procedures: guidelines for prevention, diagnosis, and treatment. Laboratory Performance Standards Committee of the Society for Cardiac Angiography and Interventions. *Cathet Cardiovasc Diagn*. 1995;34:99-104.
- Grines CL, Schreiber TL, Savas V, et al. A randomized trial of low osmolar versus nonionic contrast media in patients with myocardial infarction or unstable angina undergoing percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol*. 1996;27:1381-1386.
- Schröder R, Esch I, Ensslen R, et al. A randomized trial comparing the impact of a nonionic (Iomeprol) versus an ionic (Ioxaglate) low osmolar contrast medium on abrupt vessel closure and ischemic complications after coronary angioplasty. *J Am Coll Cardiol*. 1999;33:395-402.
- Bertrand ME, Esplugas E, Piessens J, Rasch W. Influence of a nonionic, isoosmolar contrast medium (iodixanol) versus an ionic, low-osmolar contrast medium (ioxaglate) on major adverse cardiac events in patients undergoing percutaneous transluminal coronary angioplasty: a multicenter, randomized, double-blind study. Visipaque in Percutaneous Transluminal Coronary Angioplasty [VIP] Trial Investigators. *Circulation*. 2000;101:131-136.
- Davidson CJ, Laskey WK, Hermiller JB, et al. Randomized trial of contrast media utilization in high-risk PTCA: the COURT trial. *Circulation*. 2000;101:2172-2177.
- Le Feuvre C, Batisse A, Collet JP, et al. Cardiac events after low osmolar ionic or isoosmolar nonionic contrast media utilization in the current era of coronary angioplasty. *Catheter Cardiovasc Interv*. 2006;67:852-858.
- Seeliger E, Sendeski M, Rihal CS, Persson PB. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. *Eur Heart J*. 2012;33:2007-2015.
- Levin A, Stevens PE, Bilous RW, et al. Kidney disease: improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1-150.
- Tsai TT, Patel UD, Chang TI, et al. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR cath-PCI registry. *JACC Cardiovasc Interv*. 2014;7:1-9.
- Sgura FA, Bertelli L, Monopoli D, et al. Mehran contrast-induced nephropathy risk score predicts short- and long-term clinical outcomes in patients with ST-elevation-myocardial infarction. *Circ Cardiovasc Interv*. 2010;3:491-498.
- Marenzi G, Assanelli E, Marana I, et al. N-acetylcysteine and contrast induced nephropathy in primary angioplasty. *N Engl J Med*. 2006;354:2773-2782.
- Mehran R, Owen R, Chiarito M, et al. A contemporary simple risk score for prediction of contrast-associated acute kidney injury after percutaneous coronary intervention: derivation and validation from an observational registry. *Lancet*. 2021;398:1974-1983.
- Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention. *J Am Coll Cardiol*. 2004;44:1393-1399.
- McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*. 1997;103:368-375.
- Freeman RV, O'Donnell M, Share D, et al. Nephropathy requiring dialysis after percutaneous coronary intervention and the critical role of an adjusted contrast dose. *Am J Cardiol*. 2002;90:1068-1073.
- Gurm HS, Dixon SR, Smith DE, et al. Renal function-based contrast dosing to define safe limits of radiographic contrast media in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol*. 2011;58:907-914.
- Jo SH, Youn TJ, Koo BK, et al. Renal toxicity evaluation and comparison between Visipaque (iodixanol) and Hexabrix (ioxaglate) in patients with renal insufficiency undergoing coronary angiography: the RECOVER study: a randomized controlled trial. *J Am Coll Cardiol*. 2006;48:924-930.
- Gurm HS, Seth M, Kooiman J, Share D. A novel tool for reliable and accurate prediction of renal complications in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol*. 2013;61:2242-2248.
- Briguori C, D'Amore C, De Micco F, et al. Left ventricular end-diastolic pressure versus urine flow rate-guided hydration in preventing contrast-associated acute kidney injury. *JACC Cardiovasc Interv*. 2020;13:2065-2074.
- Qian G, Fu Z, Guo J, Cao F, Chen Y. Prevention of contrast-induced nephropathy by central venous pressure-guided fluid administration in chronic kidney disease and congestive heart failure patients. *JACC Cardiovasc Interv*. 2016;9:89-96.
- Brezis M, Rosen S. Hypoxia of the renal medulla—its implications for disease. *N Engl J Med*. 1995;332:647-655.
- Persson PB, Hansell P, Liss P. Pathophysiology of contrast medium-induced nephropathy. *Kidney Int*. 2005;68:14-22.
- McDonald JS, McDonald RJ, Comin J, et al. Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. *Radiology*. 2013;267:119-128.
- Brinjikji W, Demchuk AM, Murad MH, et al. Neurons over nephrons: systematic review and meta-analysis of contrast-induced nephropathy in patients with acute stroke. *Stroke*. 2017;48:1862-1868.
- Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med*. 1994;331:1416-1420.
- Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med*. 2002;162:329-336.
- Stevens MA, McCullough PA, Tobin KJ, et al. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C.E. Study. Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. *J Am Coll Cardiol*. 1999;33:403-411.
- Brar SS, Aharonian V, Mansukhani P, et al. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. *Lancet*. 2014;383:1814-1823.
- Nijssen EC, Rennenberg RJ, Nelenmans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *Lancet*. 2017;389:1312-1322.
- Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA*. 2004;291:2328-2334.
- Briguori C, Airolidi F, D'Andrea D, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAT): a randomized comparison of 3 preventive strategies. *Circulation*. 2007;115:1211-1217.
- Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med*. 2018;378:603-614.
- Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
- Dorval JF, Dixon SR, Zelman RB, Davidson CJ, Rudko R, Resnic FS. Feasibility study of the RenalGuard™ balanced hydration system: a novel strategy for the prevention of contrast-induced nephropathy in high risk patients. *Int J Cardiol*. 2013;166:482-486.
- Briguori C, Visconti G, Focaccio A, et al. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAT II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury. *Circulation*. 2011;124:1260-1269.
- Marenzi G, Ferrari C, Marana I, et al. Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial. *JACC Cardiovasc Interv*. 2012;5:90-97.
- Marenzi G, Marana I, Lauri G, et al. The prevention of radiocontrast-agent induced nephropathy by hemofiltration. *N Engl J Med*. 2003;349:1333-1340.
- Stone GW, McCullough PA, Tumlin JA, et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA*. 2003;290:2284-2291.
- Huber W, Ilgmann K, Page M, et al. Effect of theophylline on contrast material-nephropathy in patients with chronic renal insufficiency: controlled, randomized, double-blinded study. *Radiology*. 2002;223:772-779.



47. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med.* 2000;343:180-184.
48. Subramaniam RM, Suarez-Cuervo C, Wilson RF, et al. Effectiveness of prevention strategies for contrast-induced nephropathy: a systematic review and meta-analysis. *Ann Intern Med.* 2016;164:406-416.
49. Han Y, Zhu G, Han L, et al. Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease. *J Am Coll Cardiol.* 2014;63:62-70.
50. Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F. Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome: results from the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome). *J Am Coll Cardiol.* 2014;63:71-79.
51. Andò G, Cortese B, Russo F, et al. Acute kidney injury after radial or femoral access for invasive acute coronary syndrome management: AKI-MATRIX. *J Am Coll Cardiol.* 2017;69:2592-2603.
52. Scolari F, Ravani P. Atheroembolic renal disease. *Lancet.* 2010;375:1650-1660.
53. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;79:197-215.
54. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention.* 2019;14:1435-1534.
55. James MT, Samuel SM, Manning MA, et al. Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. *Circ Cardiovasc Interv.* 2013;6:37-43.



8 Percutaneous Coronary Intervention For Unprotected Left Main Coronary Artery Disease

PHILIPPE GÉNÉREUX AND GREGG W. STONE

INTRODUCTION, 127

RANDOMIZED CONTROLLED TRIALS, 128
EXCEL and NOBLE Trials, 130

META-ANALYSES, 132

Early Meta-analyses, 132

Recent Meta-analyses After EXCEL and NOBLE, 132

CURRENT GUIDELINES AND APPROPRIATE USE CRITERIA, 132

SCORING ALGORITHMS, 134

IMPACT OF STENT CHOICE, 136

IN-STENT RESTENOSIS, 138

DISEASE LOCATION: OSTIAL OR MIDSHAFT VERSUS DISTAL LEFT MAIN CORONARY ARTERY, 139

ONE- VERSUS TWO-STENT APPROACH FOR LEFT MAIN CORONARY ARTERY BIFURCATION DISEASE, 139

TWO-STENT TECHNIQUES, 140

DEDICATED BIFURCATION STENTS, 141

IMPORTANCE OF FINAL PROXIMAL OPTIMIZATION TECHNIQUE AND SELECTIVE KISSING BALLOON INFLATION, 141

ROLE OF IMAGING, 141

Angiography, 141

Intravascular Ultrasonography, 142

Optical Coherence Tomography, 143

FRACTIONAL FLOW RESERVE, 143

MYOCARDIAL INFARCTION CAUSED BY LEFT MAIN CORONARY ARTERY THROMBOSIS, 144

HEMODYNAMIC SUPPORT, 144

DUAL ANTIPLATELET THERAPY SELECTION AND DURATION, 145

FOLLOW-UP AFTER LEFT MAIN CORONARY ARTERY PERCUTANEOUS CORONARY INTERVENTION, 145

LEFT MAIN CORONARY ARTERY BIFURCATION PCI TECHNIQUES, 145

PROVISIONAL STENT TECHNIQUE, 145

TWO-STENT TECHNIQUES, 147

DESCRIPTION OF TECHNIQUES, 147

Culotte Technique, 147

Crush Techniques, 147

T-Stent Techniques, 150

V-Stent Technique, 150

OSTIAL LEFT MAIN CORONARY ARTERY PERCUTANEOUS CORONARY INTERVENTION, 150

CONCLUSIONS, 150

Philippe Généreux: Abbott Vascular: Consultant, advisor, speaker fees; Abiomed: Consultant, advisor, speaker fees; BioTrace Medical: Consultant, advisor, speaker fees; Boston Scientific: Consultant; CARANX Medical: Consultant; Cardiovascular System Inc.: Consultant, PI Eclipse Trial; Edwards LifeSciences: Consultant, advisor, speaker fees, proctor, institutional research grant, PI EARLY-TAVR trial, PI PROGRESS trial; GE Healthcare: Consultant; iRhythm Technologies: Consultant; Medtronic: Consultant, advisor, speaker fees; Opsens: Consultant; Pi-Cardia: Equity, consultant; Puzzle Medical: Equity, consultant; Saranas: Equity, consultant; Shockwave: Consultant, speaker fees; Siemens: Consultant; Soundbite Medical Inc.: Equity, consultant; Teleflex: Consultant; 4C Medical: Consultant, PI Feasibility study; has received speaker fees from Abbott Vascular and is a consultant for Cardiovascular System, Inc.

Gregg W. Stone: Personal disclosures: Speaker honoraria from Medtronic, Abiomed, Abbott, Amgen; Consultant to Daiichi Sankyo, Ablative Solutions, Robocath, Miracor, Vectorious, Valfix, TherOx, HeartFlow, Neovasc, Ancora, Elucid Bio, Occlutech, Impulse Dynamics, Adona Medical,

Millennia Biopharma, Oxitope; Equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, Xenter Institutional disclosures: Research grants from Abbott, Abiomed, Shockwave, Vascular Dynamics, Pulnovo, Phillips, Cardiovascular Systems Inc., Biosense Webster, Bioventrix, V-wave

INTRODUCTION

Left main (LM) coronary artery disease (CAD), defined by a visually estimated diameter stenosis of at least 50%, is present in approximately 3% to 5% of patients undergoing coronary angiography.¹⁻⁵ Without revascularization, the mortality rate is as high as 50% within 3 years of follow-up.⁶⁻¹¹ Prior studies have demonstrated survival benefits of surgical revascularization of patients with significant LM disease compared with medical therapy.¹⁰⁻¹³ Current treatment guidelines recommend coronary artery bypass grafting (CABG) for most patients with unprotected

LM disease^{14,15}; however, recent evidence, paired with significant advances in stent technology, revascularization techniques, and antithrombotic therapies, have made percutaneous coronary intervention (PCI) a safe, feasible, and effective method of revascularization in many patients with LM disease, especially for patients not suitable or at high risk for open heart surgery. This chapter reviews the current evidence related to LM PCI and describes PCI techniques to manage diverse LM disease anatomy.

RANDOMIZED CONTROLLED TRIALS

To date, there have been six randomized controlled trials (RCTs) comparing PCI with CABG for LM intervention (Table 8.1)¹⁶⁻²² with follow-up to 10 years.²²⁻²⁸ LE MANS (Study of Unprotected Left Main Stenting versus Bypass Surgery) was the first RCT to compare the safety and efficacy of PCI with CABG.¹⁶ LE MANS enrolled 105 symptomatic patients with greater than 50% diameter stenosis in the LM with or without concomitant multivessel CAD to revascularization with either PCI or CABG. The primary endpoint was the change in left ventricular ejection fraction (LVEF) at 12 months as measured by two-dimensional echocardiography. The secondary endpoint was major adverse cardiac and cerebral event (MACCE), the composite of all-cause death, myocardial infarction (MI), stroke, or target vessel revascularization (TVR). At 30 days, PCI was associated with a significantly lower rate of MACCE (2% vs 13%; $P = .03$) and shorter duration of hospitalization (6.8 ± 3.7 vs 12.0 ± 9.6 days; $P = .0007$). At 1 year, LVEF improved to a significantly greater degree with PCI than with CABG ($3.3 \pm 6.7\%$ vs $0.5 \pm 0.8\%$; $P = .047$), resulting in greater LVEF in the PCI group ($58.0 \pm 6.8\%$ vs $54.1 \pm 8.9\%$;

$P = .01$). Angina status and treadmill exercise performance were comparable in the two groups. There was no difference in all-cause mortality, and 1-year MACCE rates were also similar in both groups (relative risk [RR], 1.09; 95% CI, 0.85–1.38). At 28 ± 9.9 months of follow-up, MACCE-free survival was comparable in both groups, but there was a trend of fewer deaths in the PCI group ($P = .08$). The major limitations of this trial were its small size, a relatively low rate (72%) of internal mammary artery graft use in the surgical cohort, and a high rate of bare-metal stent (BMS) use (65%), with mainly first-generation drug-eluting stents (DESs) in the remainder.

The SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) trial is the largest RCT to date to evaluate optimal revascularization strategy (PCI vs CABG) in patients with LM disease.¹⁷ SYNTAX randomized 1800 patients with three-vessel or LM disease to PCI with the first-generation TAXUS paclitaxel-eluting stents (PESs) or CABG, stratified by the presence of LM disease and medically treated diabetes. The primary endpoint was 1-year rate of MACCE (death from any cause, stroke, MI, or repeat revascularization), and patients were followed up to 5 years. The study used a hierarchical statistical approach that prespecified statistical testing on the LM subgroup only after the demonstration of noninferiority between PCI and CABG in the overall population for the primary endpoint of 1-year MACCE. Because PCI was not shown to be noninferior to CABG in the trial (1-year MACCE, 17.8% for PCI vs 12.4% for CABG; $P = .002$), the findings of the LM subgroup are considered hypothesis generating.

A total of 705 patients were enrolled with LM disease. The mean EuroSCORE of the LM cohort was 3.8, and the mean SYNTAX score was 30, consistent with complex and extensive CAD. The 1-year rate of MACCE in the LM subgroup was similar in the two groups (15.8% PCI vs 13.7% for

TABLE 8.1 Randomized Controlled Trials Comparing Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting in Patients with Left Main Coronary Artery Disease

STUDY	YEAR	PATIENTS (n)	FOLLOW-UP (y)	POPULATION	PRIMARY ENDPOINTS	PCI (%)	CABG (%)	P VALUE OR HR
LE MANS ¹⁶	2008	105	1	Stable and unstable angina	% Change in LVEF	3.3 ± 6.7	0.5 ± 0.8	$P = .047$
SYNTAX ^{17,23,29}	2009	705	5	Stable and unstable angina	Death, stroke, MI, unplanned revascularization	36.9	31.0	$P = .12$
PRECOMBAT ^{18,25}	2011	600	1	Angina, NSTEMI-ACS	Death, stroke, MI, TVR	8.7	6.7	$P = .01$
			5			17.5	14.3	$P = .26$
Boudriot et al ¹⁹	2011	201	1	Stable and unstable angina	MACE	19	13.9	$P = .19$
EXCEL ^{20,28}	2016	1905	3	Stable, unstable angina, NSTEMI-ACS	Death, stroke, MI SCAI criteria	15.4	14.7	$P = .02$ for noninferiority
	2019		5			22.0	19.2	0.13
NOBLE ²²	2020	1201	5	Stable, unstable angina, NSTEMI-ACS	Death, stroke, non-index treatment-related MI and new revascularization	28%	19%	HR, 1.58 (95% CI, 1.24–2.01). HR exceeded the limit for noninferiority of PCI compared with CABG; CABG was found to be superior to PCI for the primary composite endpoint; $P = .0002$

CABG, Coronary artery bypass grafting; EXCEL, Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; HR, hazard ratio; LE MANS, Study of Unprotected Left Main Stenting versus Bypass Surgery; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; MI, myocardial infarction; NOBLE, Nordic-Baltic-British Left Main Revascularization; NS, not significant; NSTEMI-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; RCT, randomized controlled trials; SCAI, Society for Cardiovascular Angiography and Interventions; SYNTAX, Synergy Between PCI with Taxus and Cardiac Surgery; TVR, target vessel revascularization

CABG; $P = .44$).²⁹ The 1-year rate of TVR was significantly greater in the PCI group (11.8% vs 6.5%; $P = .02$); however, the rate of stroke was significantly greater in the CABG group (2.7% vs 0.3%; $P = .009$). There were no differences in the rates of all-cause death or MI between the two groups. Comparing PCI with CABG, the 1-year MACCE rate was greater in the CABG group in patients with isolated LM or LM plus one-vessel CAD (7.5% vs 13.2%, respectively) but was greater in the PCI group in patients with LM plus two-vessel or LM plus three-vessel CAD (19.8% vs 14.4% and 19.3% vs 15.4%, respectively). When stratified by SYNTAX score tertiles (0–22, 23–32, >32), the MACCE rates in the lower two tertiles were similar between PCI and CABG; however, the highest tertile had a significantly greater MACCE rate with PCI compared with CABG.

The final 5-year results of the SYNTAX trial have been published.^{23,24} The MACCE rate did not differ significantly between the two treatment groups (36.9% for PCI vs 31.0% for CABG; $P = .12$). When stratified by SYNTAX tertiles (0–22, 23–32, >32), the MACCE rates were similar between PCI and CABG in the lower two tertiles; however, in the highest tertile, PCI had a significantly higher rate of MACCE

compared with CABG (Figure 8.1). Although these data suggest that PCI with TAXUS stents may be a reasonable alternative to CABG in patients with low and intermediate SYNTAX scores, given the small sample sizes of these subsets, prospective trials are required for confirmation before such an approach is widely adopted. The 10-year follow-up of the SYNTAX trial was recently published, showing no significant difference in all-cause death between PCI and CABG. Although CABG provided a significant survival benefit in patients with three-vessel disease, this was not shown in patients with LM CAD (153 [28%] of 546 had died after PCI vs 114 [21%] of 549 after CABG; hazard ratio [HR], 1.42; 95% CI, 1.11–1.81).²⁷

The PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) randomized 600 patients with LM disease to the first-generation Cypher sirolimus-eluting stents (SESs) versus CABG.¹⁸ The primary endpoint was MACCE (the composite of death from any cause, MI, stroke, or ischemia-driven TVR) at 1 year, powered for noninferiority. The mean EuroScore was 2.7, and the mean SYNTAX score was 25. At

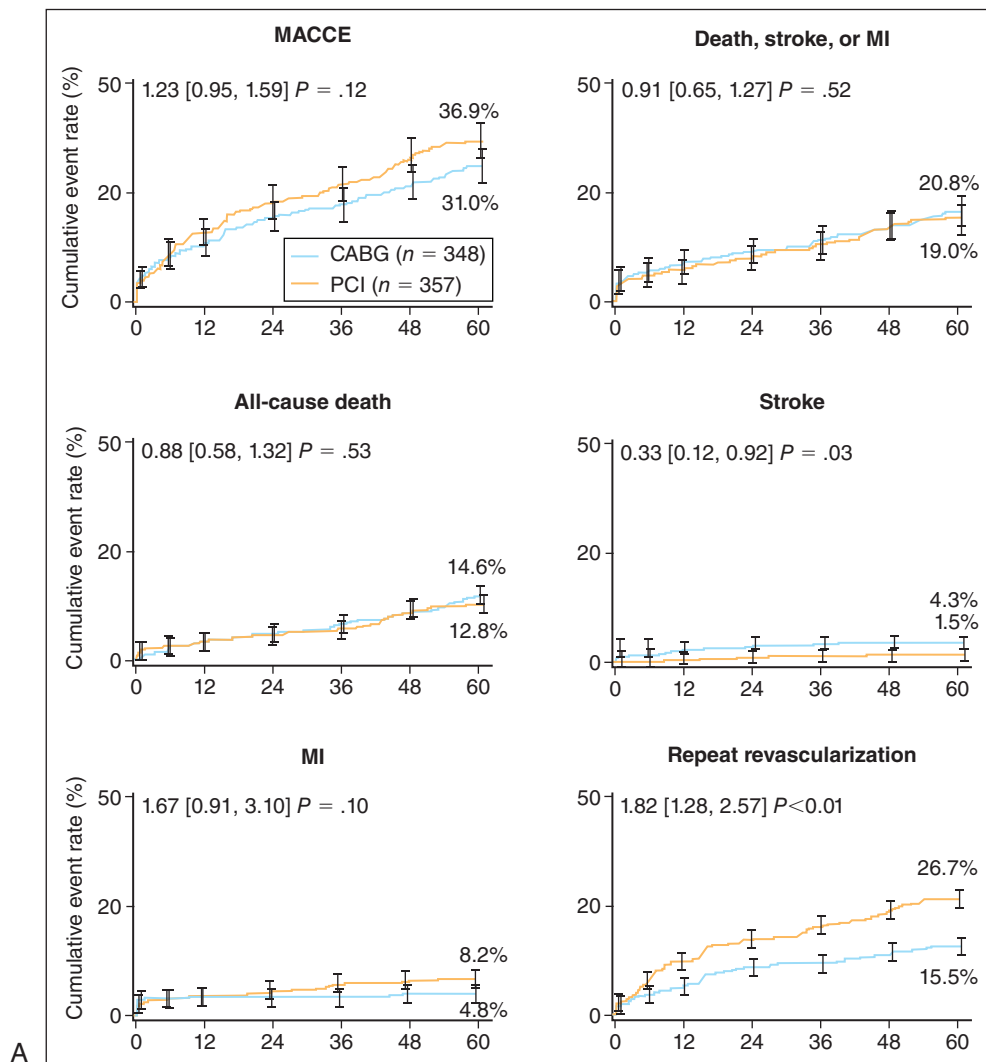


FIGURE 8.1 Final 5-year results of the SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) trial in the subgroup of patients with left main coronary artery (LM) disease ($n = 705$). (A) Five-year incidence of cardiac events in LM patients. Hazard ratio (HR) and 95% confidence intervals (CIs) are from the Cox partial likelihood method. Event rates are Kaplan-Meier estimates with a log-rank P value.

Continued

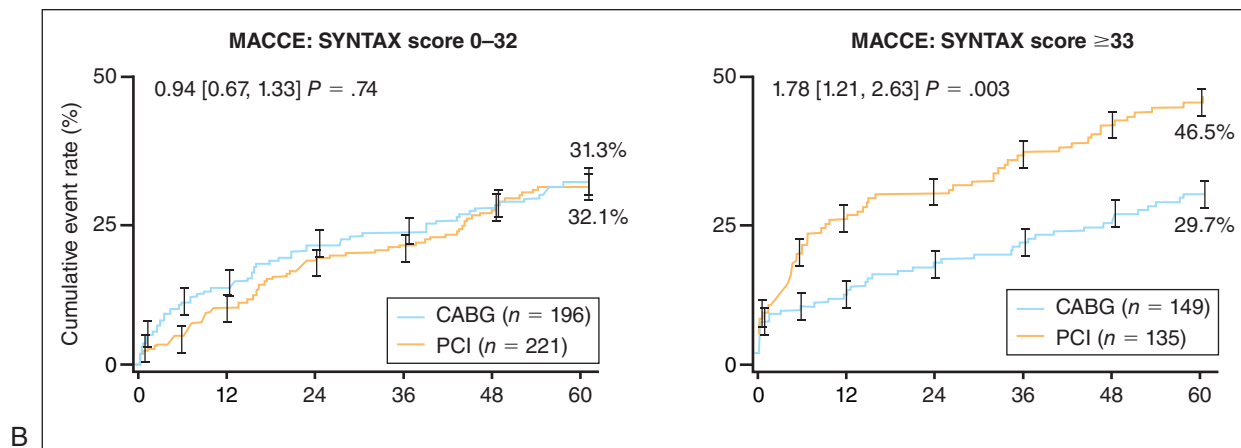


FIGURE 8.1, cont'd (B) Five-year incidence of cardiac events in patients with low and intermediate (0–32) and high (≥ 33) SYNTAX scores. HR and 95% CIs are from the Cox partial likelihood method. Event rates are Kaplan-Meier estimates with a log-rank P value. CABG, Coronary artery bypass grafting; MACCE, major adverse cardiac and cerebral event; MI, myocardial infarction; PCI, percutaneous coronary intervention. (From Morice MC, Serruys PW, Kappetein AP, et al. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation*. 2014;129:2388-2394.)

1 year, PCI was shown to be noninferior to CABG for MACCE (8.7% for PCI vs 6.7% for CABG; $P = .01$ for noninferiority). Additionally, there were no differences at 1 year in any of the individual components of the composite endpoint. At 2 years, the rate of MACCE was also not significantly different between the groups (12.2% for PCI vs 8.1% for CABG; $P = .12$), although ischemia-driven TVR was significantly more common in the PCI group (9.0% vs 4.2%; $P = .02$). The main limitations of this trial were the modest number of patients enrolled, the wide margin for noninferiority, and the low event rates in both groups, making these results hypothesis generating rather than conclusive. The 5- and 10-year results have been recently published, showing consistent findings.^{25,26} Indeed, the 10-year incidence of the composite of death, MI, or stroke (18.2% vs 17.5%; HR, 1.00; 95% CI, 0.70–1.44) and all-cause mortality (14.5% vs 13.8%; HR, 1.13; 95% CI, 0.75–1.70) were not significantly different between the PCI and CABG groups. As expected, ischemia-driven TVR was more frequent after PCI than after CABG (16.1% vs 8.0%; HR, 1.98; 95% CI, 1.21–3.21).²⁶

The fourth RCT comparing PCI with CABG in unprotected LM disease is a small study from Boudriot et al.¹⁹ This trial enrolled 201 patients with documented ischemia and LM diameter stenosis greater than 50% with or without multivessel disease. The primary clinical endpoint was the composite rate of major adverse cardiac events (MACE) at 1 year, including cardiac death, MI, or TVR, powered for noninferiority. PCI failed to reach noninferiority compared with CABG for 1-year MACE (19% PCI vs 13.9% CABG; $P = .19$ for noninferiority), driven by greater TVR after PCI. The overall results remained unchanged at extended 3-year follow-up. Major limitations of this study included a small sample size, the noninclusion of stroke as an endpoint and use of first-generation DESs.

EXCEL and NOBLE Trials

Limitations of the four prior RCTs included small numbers of patients and use of first-generation DESs. The EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial and the NOBLE

(Nordic-Baltic-British Left Main Revascularization) study represent the most recent and robust evidence in regard to LM revascularization. The EXCEL trial randomly assigned 1905 patients with LM disease of low or intermediate anatomic complexity (SYNTAX score of ≤ 32) to undergo either PCI with fluoropolymer-based cobalt–chromium everolimus-eluting stents (EESs) (PCI group, 948 patients) or CABG (CABG group, 957 patients). The primary endpoint was the rate of a composite of death from any cause, stroke, or MI at 3 years, and the trial was powered for noninferiority testing of the primary endpoint (noninferiority margin, 4.2 percentage points). At 3 years of follow-up, the primary endpoint of death, stroke, or MI occurred with similar frequency in the CABG and PCI group (14.7 vs 15.4%; HR, 1.00, 95% CI, 0.79–1.26; $P = .98$). The preplanned landmark analysis from 30 days to 3 years showed a significant difference for the primary endpoint in favor of CABG (7.9 vs 11.5%; $P = .02$).²⁰

At 5 years, the primary endpoint occurred in 22.0% of the patients in the PCI group and in 19.2% of the patients in the CABG group (difference, 2.8 percentage points; 95% CI, -0.9 to 6.5; $P = .13$). Death from any cause occurred more frequently in the PCI group than in the CABG group (in 13.0% vs 9.9%; difference, 3.1 percentage points; 95% CI, 0.2–6.1). In the PCI and CABG groups, the incidences of definite cardiovascular death (5.0% and 4.5%, respectively; difference, 0.5 percentage points; 95% CI, -1.4 to 2.5) and MI (10.6% and 9.1%; difference, 1.4 percentage points; 95% CI, -1.3 to 4.2) were not significantly different. All cerebrovascular events were less frequent after PCI than after CABG (3.3% vs 5.2%; difference, -1.9 percentage points; 95% CI, -3.8 to 0), although the incidence of stroke was not significantly different between the two groups (2.9% and 3.7%; difference, -0.8 percentage points; 95% CI, -2.4 to 0.9). Ischemia-driven revascularization was more frequent after PCI than after CABG (16.9% vs 10.0%; difference, 6.9 percentage points; 95% CI, 3.7–10.0).²⁸ No interaction was detected in regard to different SYNTAX score terciles and the primary endpoint of death, stroke, or MI at 4 year follow-up, but an interaction was observed in regard to the composite of death, stroke, MI, or unplanned revascularization, in which the relative and absolute hazard of

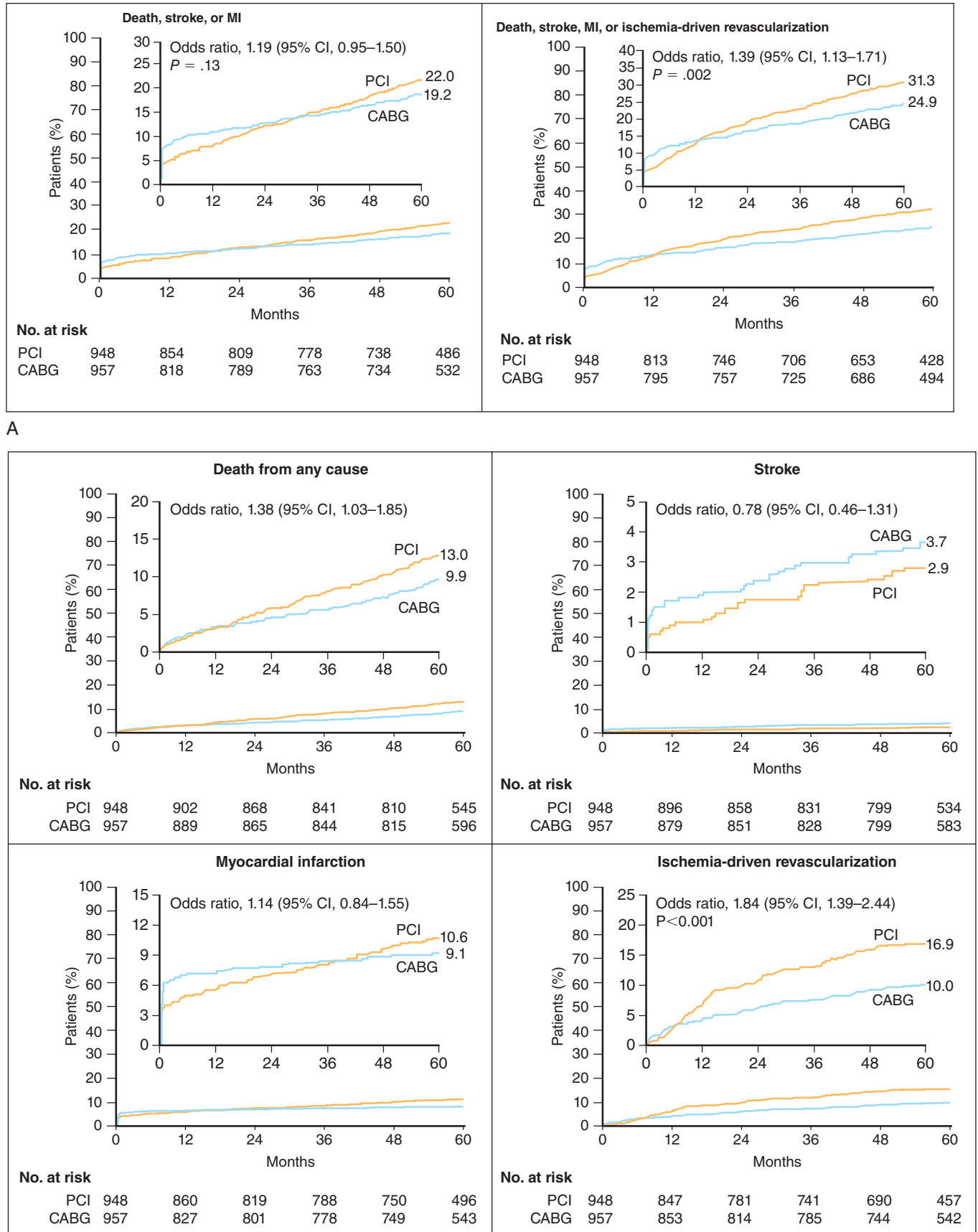


FIGURE 8.2 Five-year final results of the EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial. **A**, Time-to-first-event curves for the primary and secondary composite outcomes through 5-year follow-up. *Top panel* shows the results of the primary composite outcome of death from any cause, stroke, or myocardial infarction (MI). *Bottom panel* shows the results of the secondary composite outcome of death from any cause, stroke, MI, or ischemia-driven revascularization. Event rates were based on Kaplan-Meier estimates. **B**, Time-to-First-event curves for the components of the primary and secondary composite outcomes through 5-year follow-up. Results of analyses of the components of the primary and secondary composite outcomes are shown. CABG, Coronary artery bypass grafting; CI, confidence interval; PCI, percutaneous coronary intervention. (From Stone GW, Kappetein AP, Sabik JF, et al. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med*. 2019;381:1820-1830.)



MACCE with PCI compared with CABG rose progressively with the SYNTAX score³⁰ (Figure 8.2).

The NOBLE (Nordic-Baltic-British Left Main Revascularization) trial compared CABG with PCI using new-generation DES (biolimus-eluting stents [BESs]) among 1201 patients with significant LM disease (mean SYNTAX score, 23). The primary endpoint was a composite of all-cause mortality, nonprocedural MI, any repeat coronary revascularization, or stroke. Noninferiority of PCI to CABG required the lower end of the 95% CI not to exceed an HR of 1.35 after up to 5 years of follow-up. The intention-to-treat principle was used in the analysis if not specified otherwise. At a median follow-up period of 3.1 years, Kaplan-Meier 5-year estimates of MACCE were 28% for PCI (121 events) and 18% for CABG (80 events) (HR, 1.51; 95% CI, 1.13–2.00), exceeding the limit for noninferiority, and CABG was deemed significantly better than PCI ($P = .0044$). As-treated estimates were 28% versus 18% (HR, 1.48; 95% CI, 1.11–1.98; $P = .0069$). Comparing PCI with CABG, 5-year estimates were 11% vs 9% (HR, 1.08; 95% CI, 0.67–1.74; $P = .84$) for all-cause mortality, 6% vs 2% (HR, 2.87; 95% CI, 1.40–5.89; $P = .0040$) for nonprocedural MI, 15% vs 10% (HR, 1.50; 95% CI, 1.04–2.17; $P = .0304$) for any revascularization, and 5% vs 2% (HR, 2.20; 95% CI, 0.91–5.36; $P = .08$) for stroke.²¹ Five-year follow-up demonstrated similar findings. Indeed, at a median of 4.9 years of follow-up, Kaplan-Meier 5-year estimates of MACCE were 28% (165 events) for PCI and 19% (110 events) for CABG (HR, 1.58; 95% CI, 1.24–2.01); the HR exceeded the limit for noninferiority of PCI compared with CABG. CABG was found to be superior to PCI for the primary composite endpoint ($P = .0002$). All-cause mortality was estimated in 9% after PCI versus 9% after CABG (HR, 1.08; 95% CI, 0.74–1.59; $P = .68$), nonprocedural MI was estimated in 8% after PCI versus 3% after CABG (HR, 2.99; 95% CI, 1.66–5.39; $P = .0002$), and repeat revascularization was estimated in 17% after PCI versus 10% after CABG (HR, 1.73; 95% CI, 1.25–2.40; $P = .0009$).²² Interestingly, no interaction was observed in regard to the SYNTAX score terciles, pointing toward a benefit of CABG over PCI for all anatomical complexity (Figure 8.3).

The differences between the findings of the EXCEL and NOBLE trials are most likely explained by different design and endpoint definitions, especially peri- and postprocedural MI. That being said, although CABG may have a benefit in terms of revascularization and MI, no differences in mortality (all-cause and cardiovascular) or stroke were observed in these two trials.

META-ANALYSES

Early Meta-analyses

Several meta-analyses of observational registries and RCTs have been conducted comparing PCI and CABG for LM revascularization.^{31–33} Most of these meta-analyses preceded the EXCEL and NOBLE trials and enrolled mainly patients with first-generation DESs. These early meta-analyses demonstrated similar outcomes in terms of mortality and cardiovascular death but with an increased risk of stroke with CABG and an increased risk

of unplanned revascularization for PCI. When stratifying patients by complexity and extent of baseline coronary disease by SYNTAX score assessment, PCI and CABG had nonsignificantly different rates of all-cause mortality, MI, and MACCE in the lower two tertiles of the SYNTAX score (<32); however, with more complex disease (SYNTAX score >32), CABG was associated with significantly better outcomes at 3 years. The combination of randomized trials and registries (which dominated the numbers of patients) limits the interpretation of these meta-analyses.

Recent Meta-analyses After EXCEL and NOBLE

After the publication of the EXCEL and NOBLE trials, several groups have performed meta-analyses using different methodologies.^{34–37} Table 8.2 shows the most recent meta-analyses. Although methodologies and findings may differ slightly, the main findings mirror those of the two largest randomized trials: (1) no significant difference in overall death or cardiac death was observed between PCI and CABG up to 5 years of follow-up; (2) a higher rate of unplanned revascularization during follow-up was observed with PCI compared with CABG; and (3) differences in stroke and MI were observed, with PCI showing increased procedural and spontaneous MI post-PCI, and CABG showing an increase in stroke, especially within the first year after revascularization. Different endpoint definitions impacted findings related to peri- and postprocedural MI and most likely explained the discrepancy in findings through the pooled trials.

In summary, updated meta-analyses, including most recent randomized trials of LM revascularization comparing PCI with CABG, demonstrated that PCI with DES was associated with a similar risk of major cardiovascular outcomes, including all-cause mortality or cardiovascular mortality rates compared with CABG. Decisions for PCI versus CABG for LM disease should be based on weighing the upfront morbidity and mortality risk of CABG with late risk of repeat revascularization with PCI and taking into consideration patient preference.

CURRENT GUIDELINES AND APPROPRIATE USE CRITERIA

The evidence from recent RCTs and meta-analyses has been reflected in the current guidelines^{14,15,38} (Tables 8.3 to 8.5). The 2021 American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines for coronary artery revascularization focus on several key issues: (1) the importance of shared decision making incorporating the patient's preferences and beliefs; (2) the role of the heart team in facilitating these decisions; (3) the indications for revascularization to improve survival; (4) situations when one therapy is preferred over another; and (5) the use of intravascular imaging to assess patients with intermediate disease and, when PCI is planned, the use of imaging to guide PCI

(see Table 8.3).^{14,39} The Appropriate Use Criteria recommendations have also evolved to incorporate the long-term evidence from randomized clinical trial data.³⁸ Table 8.4 summarizes the recommendations. The 2018 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularization emphasize (1) the use of

established risk scores to estimate operative risk (Society of Thoracic Surgeons [STS] Class I, Level of Evidence [LOE]: B; EuroSCORE II Class II, LOE: B); (2) the calculation of the SYNTAX score to determine anatomic complexity (Class I, LOE: B); (3) the importance to achieve complete revascularization (Class IIa, LOE: B); and (4) the heart team approach (Class I, LOE: C) (see Table 8.5).¹⁵

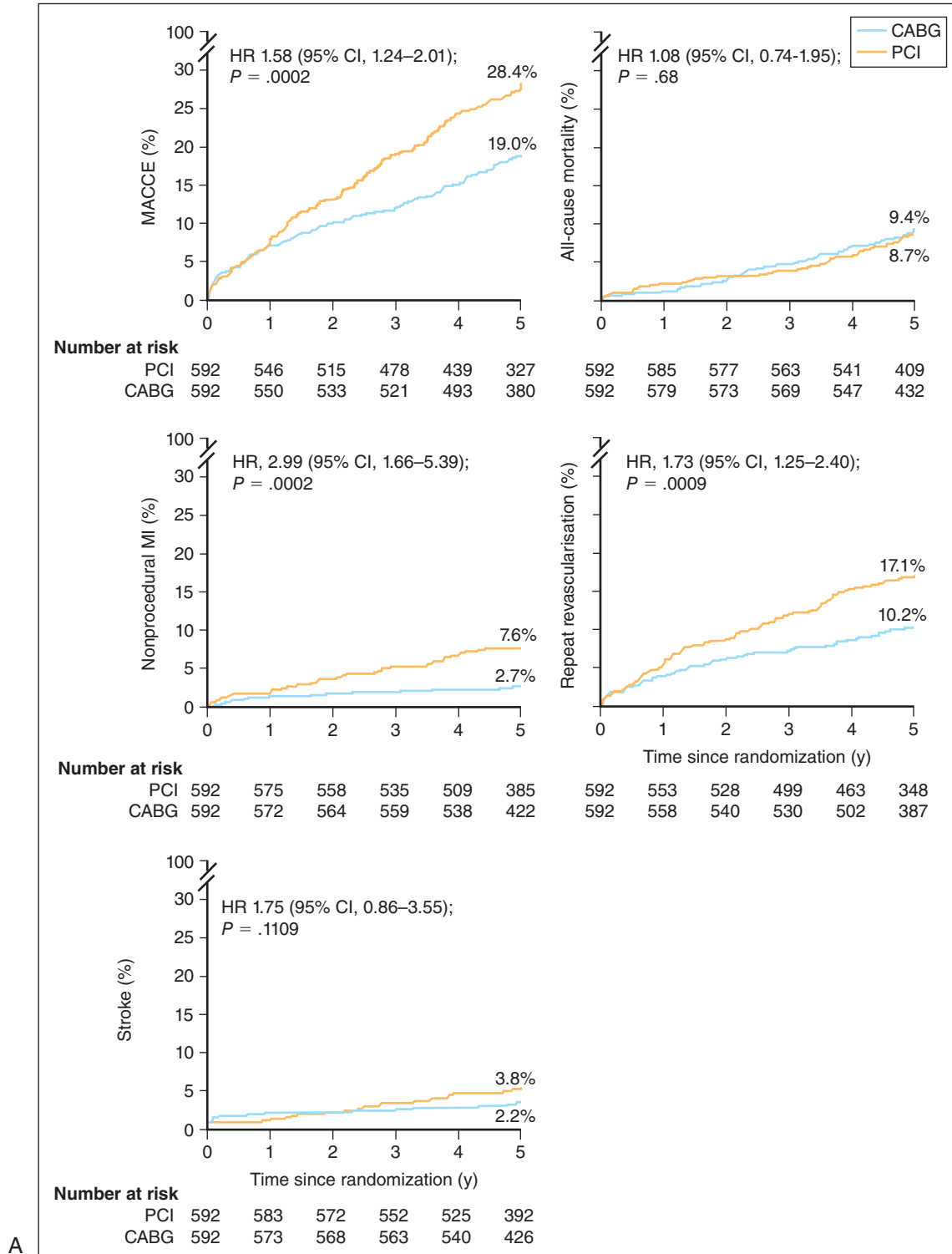


FIGURE 8.3 Five-year results of the NOBLE (Nordic-Baltic-British Left Main Revascularization) trial. **A**, Kaplan-Meier estimates of 5-year clinical outcomes in intention-to-treat population.

Continued

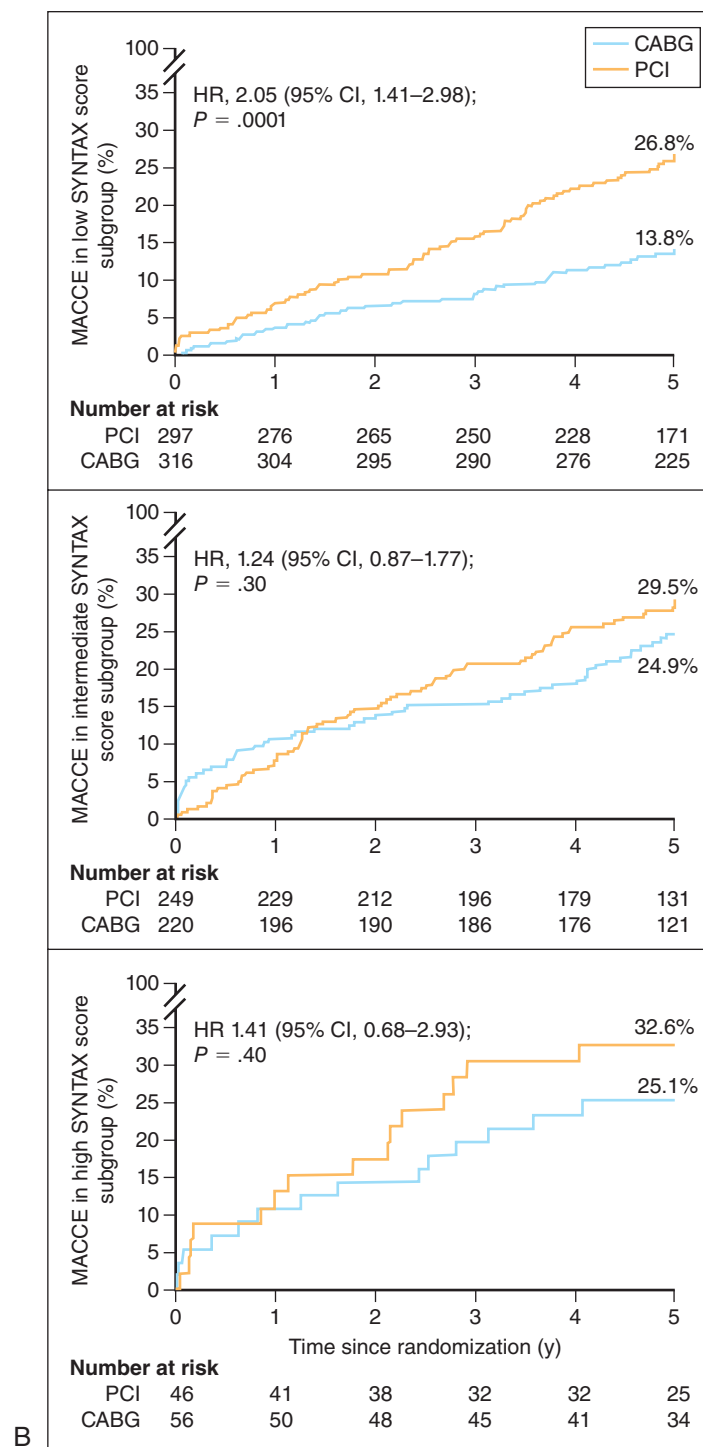


FIGURE 8.3, cont'd B, Results stratified by SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score tertiles. Kaplan-Meier estimates of major adverse cardiac and cerebrovascular events (MACCE) by SYNTAX score subgroup. A low score is defined as 1 to 22, intermediate is 23– to 32, and high is 33 or more. CABG, Coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention. (From Holm NR, Makikallio T, Lindsay MM, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. *Lancet*. 2020;395:191-199.) PCI

SCORING ALGORITHMS

Scoring algorithms to assess clinical risk and anatomic disease complexity bring objectivity to risk stratification and, paired with clinical judgment, can guide the decision-making process to select the most appropriate revascularization strategy for a given patient. The clinical STS and EuroSCORE II are recommended to assess suitability for

CABG, whereas the anatomic SYNTAX score is useful to discriminate relative outcomes between PCI and CABG.¹⁵

The SYNTAX score, first developed and evaluated in the SYNTAX trial,¹⁷ was subsequently validated and studied in many unprotected LM studies.^{29,92-98} In most of these studies, rates of composite ischemic endpoints (death, MI, target lesion revascularization [TLR], or TVR) were significantly greater after PCI in the highest tertile of SYNTAX

TABLE 8.2 Recent Meta-analyses Comparing Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting in Patients with Left Main CORONARY ARTERY Disease

AUTHORS	YEAR	PATIENTS (n)	TRIALS POOLED	METHODOLOGY	FOLLOW-UP	DEATH	CARDIAC DEATH	STROKE	MI	UNPLANNED REVASCULARIZATION
Ahmad et al ³⁴	2020	4612	PRECOMBAT, ²⁵ 5 y SYNTAX, ²⁷ 10 y Boudriot et al. ¹⁹ 1 y EXCEL, ²⁸ 5 y NOBLE, ²² 5 y	Study level	67.1 mo	PCI vs CABG RR, 1.03; 95% CI, 0.82–1.30; P = .779	PCI vs CABG RR, 1.03; 95% CI, 0.79–1.34; P = .817	PCI vs CABG RR, 0.74; 95% CI, 0.36–1.50; P = .400	PCI vs CABG RR, 1.22; 95% CI, 0.96–1.56; P = .110	PCI vs CABG RR, 1.73; 95% CI, 1.49–2.02; P < .001
Kuno et al ³⁶	2020	4394	SYNTAX, ²⁷ 10 y PRECOMBAT, ²⁶ 10 y EXCEL, ²⁸ 5 yr NOBLE, ²² 5 yr	Study level	≥5 y	PCI vs CABG HR, 1.11; 95% CI, 0.91–1.35; P = .30	PCI vs CABG HR, 1.13; 95% CI, 0.88–1.44; P = .34	PCI vs. CABG HR, 0.81; 95% CI, 0.42–1.53; P = .53	PCI vs CABG HR, 1.48; 95% CI, 0.88–2.48; P = .14	PCI vs CABG HR, 1.80; 95% CI, 1.52–2.13; P < .01
Sabatine et al ³⁷	2021	4394	SYNTAX, ^{17,23,24,29} PRECOMBAT ^{18,25} EXCEL ^{20,28} NOBLE ^{21,22}	Patient level	5 y	Kaplan-Meier estimate of 5-y all-cause death was 11.2% (95% CI, 9.9–12.6) with PCI and 10.2% (95% CI, 9.0–11.6) with CABG (HR, 1.10; 95% CI, 0.91–1.32; P = .33)	PCI vs CABG 6.2% (95% CI, 5.3–7.4) vs 5.9% (95% CI, 4.9–7.0) HR, 1.07; 95% CI, 0.83–1.37; P = .61	Overall, no difference PCI (2.7%; 95% CI, 2.0–3.5) vs CABG (3.1%, 95% CI, 2.4–3.9); HR, 0.84, 95% CI, 0.59–1.21; P = .36, but the risk was lower with PCI in the first year after randomization (HR, 0.37; 95% CI, 0.19–0.69)	Spontaneous MI PCI (6.2%; 95% CI, 5.2–7.3) vs CABG (2.6%; 95% CI, 2.0–3.4); HR, 2.35; 95% CI, 1.71–3.23; P < .0001	PCI vs CABG PCI (18.3%; 95% CI, 16.7–20.0) vs CABG (10.7%, 95% CI, 9.4–12.1); HR, 1.78; 95% CI, 1.51–2.10; P < .0001
Gallo et al ³⁵	2022	4595	PRECOMBAT ²⁵ SYNTAX ²³ Boudriot et al. ¹⁹ EXCEL ²⁸ NOBLE ²²	Study level	5 y	PCI vs CABG OR, 1.13; 95% CI, 0.93–1.38; P = .21	PCI vs CABG OR, 1.09; 95% CI, 0.84–1.41; P = .21	PCI vs CABG OR, 0.88; 95% CI, 0.61–1.28; P = .51	PCI vs CABG OR, 1.43; 95% CI, 1.13–1.79; P = .003	PCI vs CABG OR, 1.89; 95% CI, 1.58–2.26; P < .001

CABG, Coronary artery bypass grafting; CI, confidence interval; EXCEL, Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NOBLE, Nordic-Baltic-British Left Main Revascularization; OR, odds ratio; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; RR, relative risk; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

TABLE 8.3 The American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions 2021 Guidelines for Percutaneous Coronary Intervention in Unprotected Left Main Coronary Artery Disease

COR	LOE	RECOMMENDATION
I	C-LD	In patients undergoing revascularization, decisions should be patient centered—that is, considerate of the patient's preferences and goals, cultural beliefs, health literacy, and social determinants of health—and made in collaboration with the patient's support system. ^{40,41}
I	C-LD	In patients undergoing coronary angiography or revascularization, adequate information about the benefits, risks, therapeutic consequences, and potential alternatives in the performance of percutaneous and surgical myocardial revascularization should be given, when feasible, with sufficient time for informed decision making to improve clinical outcomes. ⁴²⁻⁴⁴
I	B-NR	In patients for whom the optimal treatment strategy is unclear, a heart team approach that includes representatives from interventional cardiology, cardiac surgery, and clinical cardiology is recommended to improve patient outcomes. ⁴⁵⁻⁵¹
I	B-R	In patients with stable ischemic heart disease and significant LM stenosis, CABG is recommended to improve survival. ^{9,11,52,53}
I	B-R	In patients who require revascularization for significant LM CAD with high-complexity CAD, it is recommended to choose CABG over PCI to improve survival. ^{23,29}
IIa	B-NR	In selected patients with stable ischemic heart disease and significant LM stenosis for whom PCI can provide equivalent revascularization to that possible with CABG, PCI is reasonable to improve survival. ⁵²
IIa	B-NR	In patients with intermediate stenosis of the LM artery, IVUS is reasonable to help define lesion severity. ⁵⁴⁻⁵⁸
IIa	B-R	In patients undergoing coronary stent implantation, IVUS can be useful for procedural guidance, particularly in cases of LM or complex coronary artery stenting, to reduce ischemic events. ⁵⁹⁻⁶⁸
IIa	B-R	In patients undergoing coronary stent implantation, OCT is a reasonable alternative to IVUS for procedural guidance, except in ostial LM disease. ⁶⁹⁻⁷¹
IIb	B-NR	In patients with multivessel CAD, an assessment of CAD complexity, such as the SYNTAX score, may be useful to guide revascularization. ^{72,73}
IIb	B-R	In patients with diabetes who have LM stenosis and low- or intermediate-complexity CAD in the rest of the coronary anatomy, PCI may be considered an alternative to CABG to reduce major adverse cardiovascular outcomes. ^{74,75}
IIb	B-R	In selected high-risk patients, elective insertion of an appropriate hemodynamic support device as an adjunct to PCI may be reasonable to prevent hemodynamic compromise during PCI. ^{76,77}

B-NR, B-nonrandomized; B-R, B-randomized; CABG, coronary artery bypass graft; CAD, coronary artery disease; C-LD, C-limited data; COR, class of recommendation; IVUS, intravascular ultrasound; LM, left main coronary artery; LOE, level of evidence; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

Adapted from Writing Committee M, Lawton JS, Tamis-Holland JE et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:197-215.

score than in the lower 2 tertiles. Capodanno et al.⁹³ demonstrated that a SYNTAX score greater than 34 was associated with significantly higher rates of ischemic events in patients with LM CAD undergoing PCI than in those undergoing CABG. Of note, only the baseline SYNTAX score had prognostic value; the lesion location in the LM (ostial, shaft, or bifurcation) and number of stents implanted were not predictive of clinical outcomes. Similarly, analysis from the Drug-eluting-stents for Unprotected Left Main Stem Disease (ISAR-Left Main) trial also showed a clear association between the overall burden and complexity of CAD, as assessed by SYNTAX score, and the rate of TLR and MACE at 3 years.⁹⁹

By combining clinical variables and the angiographic SYNTAX score, several other scores have been created and studied in an attempt to improve the predictive capability of the solely anatomic SYNTAX score. Of note, the Global Risk Classification, which is a combination of the SYNTAX score and EuroSCORE, showed the best calibration and discrimination in the prediction of adverse events such as mortality after LM PCI.¹⁰⁰ Additionally, the Global Risk Classification identified a low-risk cohort of patients (low SYNTAX score) who could be safely treated with PCI.¹⁰¹

The recently developed SYNTAX Score II combines the SYNTAX score with anatomic and clinical variables that were shown to alter the threshold value at which equipoise was achieved between CABG and PCI for long-term mortality.¹⁰² The variables included are age, creatinine clearance, LVEF, presence of unprotected LM disease (vs three-vessel

CAD), peripheral vascular disease, female sex, and chronic obstructive pulmonary disease. This score may be used to identify some patients considered to be at low risk by the anatomic SYNTAX score who might preferentially benefit from CABG and some patients considered to be at high risk by the anatomic SYNTAX score who might preferentially benefit by PCI. Further validation of the SYNTAX Score II (including assessment of endpoints other than mortality) is required before its widespread adoption.¹⁰³

IMPACT OF STENT CHOICE

Given the fact that 70% or more of the myocardial mass is typically perfused by the LM, stent failure, such as restenosis and stent thrombosis, may have potentially catastrophic consequences.¹⁰⁴ Despite its large diameter, disease involving the LM frequently involves the distal bifurcation and side branches (SBs). Table 8.6 presents data from observational registries and trials comparing different stent types for LM PCI. A meta-analysis of observational studies and RCTs involving 10,342 patients demonstrated lower event rates for DES than BMSs for mortality, repeat revascularization, and MACE at 6 to 12 months, 2 years, and 3 years. Adjusted analyses among 5081 patients demonstrated a significantly lower risk of mortality with DESs at 2-year (OR, 0.42; 95% CI, 0.28–0.62; $P < .001$) and 3-year (OR, 0.70; 95% CI, 0.53–0.92; $P < .01$) follow-up. Although these analyses should be seen as hypothesis generating, given their

TABLE 8.4 Appropriate Use Score for Left Main Coronary Artery Revascularization

Indication	ASYMPTOMATIC NOT ON AA THERAPY OR WITH AA THERAPY		NOT ON AA THERAPY		ISCHEMIC SYMPTOMS ON ONE AA DRUG (BB PREFERRED)		ON TWO OR MORE AA DRUGS	
	PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG
Isolated LM Ostial or midshaft	M (6)	A (8)	A (7)	A (8)	A (7)	A (9)	A (7)	A (9)
Isolated LM Bifurcation involvement	M (5)	A (8)	M (5)	A (8)	M (5)	A (9)	M (6)	A (9)
LM disease Ostial or midshaft Concurrent multivessel disease Low disease burden (e.g., one or two additional focal stenoses, SYNTAX score ≤ 22)	M (6)	A (8)	M (6)	A (9)	A (7)	A (9)	A (7)	A (9)
LM disease Ostial or midshaft Concurrent multivessel disease Intermediate or high disease burden (e.g., one or two additional bifurcation stenosis, long stenoses, SYNTAX score > 22)	M (4)	A (9)	M (4)	A (9)	M (4)	A (9)	M (4)	A (9)
LM disease Bifurcation involvement Low disease burden in other vessels (e.g., one or two additional focal stenosis, SYNTAX score ≤ 22)	M (4)	A (8)	M (5)	A (8)	M (5)	A (9)	M (6)	A (9)
LM disease Bifurcation involvement Intermediate or high disease burden in other vessels (e.g., one or two additional bifurcation stenosis, long stenoses, SYNTAX score > 22)	R (3)	A (8)	R (3)	A (9)	R (3)	A (9)	R (3)	A (9)

The numbers in parentheses next to the ratings reflect the median score those that indications.

A coronary revascularization is appropriate care when the potential benefits, in terms of survival or health outcomes (symptoms, functional status, and/or quality of life), exceed the potential negative consequences of the treatment strategy. The rating panel scored each indication on a scale from 1 to 9 as follows: Score 7–9 = Appropriate care; Score 4–6 = May be appropriate care; and Score 1–3 = Rarely appropriate care.

A, Appropriate; AA, antianginal; BB, beta-blocker; CABG, coronary artery bypass grafting; LM, left main coronary artery; M, may be appropriate; PCI, percutaneous coronary intervention; R, rarely appropriate; and SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery trial.

Adapted from Patel MR, Calhoun JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;69(17):2212-2241.

TABLE 8.5 The 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines on Myocardial Revascularization for Unprotected Left Main Coronary Artery Disease

COR	LOE	RECOMMENDATION
I	B	It is recommended that the STS score is calculated to assess in-hospital or 30-day mortality rate and in-hospital morbidity after CABG. ⁷⁸⁻⁸⁰
I	B	In patients with LM or multivessel disease, it is recommended that the SYNTAX score is calculated to assess the anatomic complexity of CAD and the long-term risk of mortality and morbidity after PCI. ^{23,24,29,72,74,81-85}
I	A	Indications for revascularization in patients with stable angina or silent ischemia with LM disease with stenosis $> 50\%$ to improve prognosis. ^{9,52,86,87}
I	A	Revascularization with CABG for LM disease with low (0–22), intermediate (23–32), and high SYNTAX scores (≥ 33). ^{23-25,32,52,74,88,89}
I	A	Revascularization with PCI for LM disease with low SYNTAX score (0–22). ^{23-25,32,52,74,88,89}
IIa	A	Revascularization with PCI for LM disease with intermediate (23–32) SYNTAX score. ^{23-25,32,52,74,88,89}
IIa	B	IVUS should be considered to assess the severity of unprotected LM lesions. ^{54,58,90}
IIa	B	IVUS should be considered to optimize treatment of unprotected LM lesions. ⁹⁰
IIa	C	It should be considered that PCI for LM be performed by trained operators with an annual volume of ≥ 25 LM PCI cases per year.
IIa	C	It should be considered that nonemergency high-risk PCI procedures—such as for LM disease, single remaining patent coronary artery, and complex chronic total occlusions—are only performed by adequately experienced operators at centers that have access to circulatory support and intensive care treatment.
IIa	C	It should be considered that CABG be performed at institutions with annual institutional volumes of ≥ 200 CABG cases.
IIb	B	Calculation of the EuroSCORE II score may be considered to assess in-hospital mortality after CABG. ⁷⁸
IIb	B	In true bifurcation lesions of the left main, the double-kissing crush technique may be preferred over provisional T-stenting. ⁹¹
IIb	C	Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting (e.g., history of stent thrombosis or left main stenting).

Continued

TABLE 8.5 The 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines on Myocardial Revascularization for Unprotected Left Main Coronary Artery Disease—cont'd

COR	LOE	RECOMMENDATION
IIb	C	After high-risk PCI (e.g., unprotected LM stenosis), late (3–12 mo) surveillance angiography may be considered, irrespective of symptoms.
III	B	Revascularization with PCI for LM disease with high (≥ 33) SYNTAX score ^{a23–25,32,52,74,88,89}

^aPercutaneous coronary intervention (PCI) should be considered if the heart team is concerned about the surgical risk or if the patient refuses coronary artery bypass grafting (CABG) after adequate counselling by the heart team.

CAD, Coronary artery disease; COR, class of recommendation; IVUS, intravascular ultrasound; LM, left main; LOE, level of evidence; PCI, Society of Thoracic Surgeons; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

Adapted from Neumann FJ, Sousa-Uva M, Ahlsson A et al. The 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.

TABLE 8.6 Randomized Trials and Large Observational Studies Comparing Stent Types in Left Main Coronary Artery Percutaneous Coronary Intervention

STUDY	YEAR	PATIENTS (n)	TYPE	FOLLOW-UP	STENT TYPE	PRIMARY OUTCOME	PRIMARY OUTCOME	TVR/TLR	STENT THROMBOSIS
BMS vs DES									
Erglis et al. ¹⁰⁵	2007	103	RCT	6 mo	BMS vs PES	Freedom from death, MI, and TLR	70.0% vs 86.8%; <i>P</i> = .036	16.0% vs 2.0%; <i>P</i> = .014	—
Palmerini et al. ¹⁰⁴	2008	1453	NR	2 y	BMS vs DES	Freedom from cardiac death	82.4% vs 93.1%; <i>P</i> = .00001	—	—
Kim et al. ¹⁰⁶	2009	1217	NR	3 y	BMS vs DES	Death or MI	14.9% vs 14.3%; <i>P</i> = .85	12.1% vs 5.4%; <i>P</i> < .001	—
Onuma et al. ⁹⁵	2010	227	NR	4 y	BMS vs SES or PES	Death, MI, or TVR	53.2% vs 51.4%; <i>P</i> = .9	13.9% vs 16.2%; <i>P</i> = .7	—
Brennan et al. ⁴	2012	2765	NR	2.5 y	BMS vs DES	Death	52.7% vs 39.6%; <i>P</i> = significant	—	—
DES vs DES									
ISAR-LM ¹⁰⁷	2009	607	RCT	1 y	PES vs SES	Death, MI, or TLR	13.6% vs 15.8%; <i>P</i> = .44	6.5% vs 7.8%; <i>P</i> = .49	0.3% vs 0.7%; <i>P</i> = .57
ISAR-LM II ¹⁰⁸	2013	650	RCT	1 y	ZES vs EES	Death, MI, or TLR	17.5% vs. 14.3%; <i>P</i> = .25	11.7% vs 9.4%; <i>P</i> = .35	0.9% vs. 0.6%; <i>P</i> = .99
PRECOMBAT II ¹⁰⁹	2012	661	NR	1.5 y	EES vs SES	Death, MI, stroke, or TVR	8.9% vs 10.8%; <i>P</i> = .51	6.5% vs 8.2%; <i>P</i> = .65	0% vs 0.3%; <i>P</i> = .11
LEMAX ¹¹⁰	2013	344	NR	2 y	EES vs PES	TLF	7.6% vs 16.3%; <i>P</i> = .01	—	1.7% vs 7.0% ^a ; <i>P</i> = .01

^aReported as definite, probable, or possible stent thrombosis.

BMS, Bare-metal stent; DES, drug-eluting stent; EES, everolimus-eluting stent; ISAR, intracoronary stenting and angiographic results; LEMAX, left main XIENCE; LM, left main; MI, myocardial infarction; NR, nonrandomized; PES, paclitaxel-eluting stent; PRECOMBAT, premier of randomized comparison of bypass surgery versus angioplasty using sirolimus-eluting stent in patients with left main coronary artery disease; RCT, randomized control trial; SES, sirolimus-eluting stent; TLF, target lesion failure (cardiac death, target vessel MI, and target lesion revascularization); TLR, target lesion revascularization; TVR, target vessel revascularization; ZES, resolute zotarolimus-eluting stent.

retrospective nature, these data support a default strategy of DES for LM PCI in most cases unless long-term dual antiplatelet therapy (DAPT) is contraindicated.¹¹¹

To date, only two RCTs have compared different DESs in LM PCI.^{107,108} In ISAR-Left Main, no significant difference in the 1-year composite endpoint of death, MI, or TLR was present between Cypher SES and Taxus PES (both first-generation DES).¹⁰⁷ Similarly, no difference in the same endpoint was observed in ISAR-Left Main II between slow-release resolute zotarolimus-eluting stents (ZES) and everolimus-eluting stents (EESs) (both second-generation DESs).¹⁰⁸ The modest number of patients included in these studies (~600), however, precludes definitive conclusions. Recently, a retrospective study demonstrated better mid-term (2-year) outcomes when comparing a first-generation DES (PES) with a second-generation DES (EES) in terms of target vessel failure (a composite of cardiac death, target vessel MI, or TLR).¹¹⁰ Again, given the small number of patients included in this study (*n* = 344) and the retrospective

nature of the analysis, these results are hypothesis generating. That being said, in light of the important burden of evidence supporting the improved safety and efficacy of second-generation DES compared with both first-generation DESs and BMSs,^{112,113} second-generation DES should be the default platform when performing unprotected LM PCI, assuming the absence of contraindication to their use.^{14,15}

IN-STENT RESTENOSIS

No dedicated RCTs examining treatment options of LM in-stent restenosis (ISR) have been conducted so far, and most of the current evidence has originated from registry data and observational series. In the CORPAL (Córdoba and Las Palmas) registry, 7% of patients who underwent PCI with DESs in unprotected LM disease developed ISR at a median follow-up of 9 months.¹¹⁴ The location of restenosis was divided equally among the main vessel (MV) (LM or left

anterior descending coronary artery [LAD]) or isolated to the ostium of circumflex or both arteries. Angiographically, ISR lesions were divided equally between focal (47%) and diffuse (51%). Intravascular ultrasonography (IVUS) was conducted in 79% of patients with ISR and demonstrated that stent underexpansion was present in 14% of the cases. All patients except four were treated with repeat PCI with DESs—58% with provisional stenting and 42% with a two-stent approach. During a follow-up period of 4 years, the overall recurrent MACE rate was 22%, with the provisional approach having a significantly higher MACE-free survival compared with the two-stent approach (85% vs 53%; $P < .05$). Similarly, patients with ISR involving only one bifurcation segment had better MACE-free survival compared with patients with more than one segment involved (84% vs 47%; $P < .05$) at 4 years.

In the MITO (Milan and New-Tokyo) registry, 92 of 474 (19%) unprotected LM patients undergoing PCI with DES developed ISR, and 84 (19%) were treated with repeat PCI (43 with balloon angioplasty alone and 41 with further DES implantation).¹¹⁵ Of note, patients with focal left circumflex (LCX) stenosis were frequently asymptomatic and were discovered only on angiographic follow-up. During a follow-up period of 2 years, the patients undergoing plain old balloon angioplasty had significantly greater MACE rates compared with repeat PCI with DESs (HR, 2.75; 95% CI, 1.26–5.98; $P = .01$).

One of the important independent predictors of LM ISR is the final minimum stent area as determined by IVUS.¹¹⁶ Post-PCI optimal values for the MV, both branches, and the polygon of confluence (POC) have been established and were shown to be associated with significantly improved outcomes (Figure 8.4).

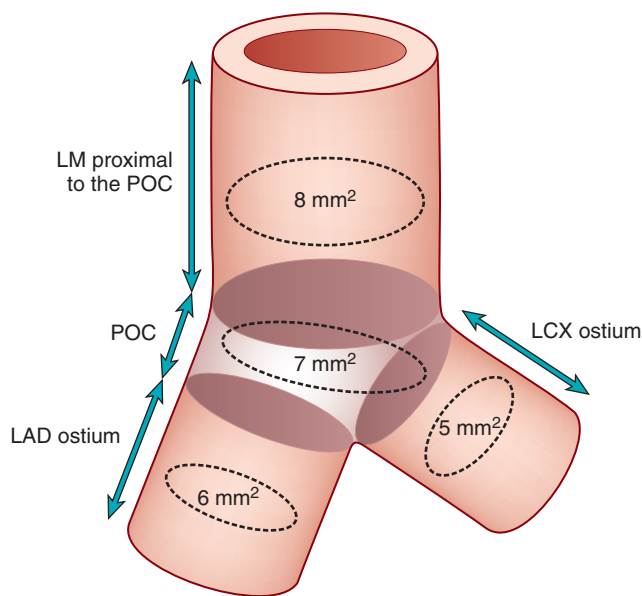


FIGURE 8.4 Approximate values for the intravascular ultrasound-derived minimal lumen area (MLA) for different coronary segments associated with freedom from restenosis and major adverse ischemic events at 2 years after left main coronary artery (LM) stenting in Korea. LAD, Left anterior descending; LCX, left circumflex; POC, polygon of confluence. (Adapted from Kang SJ, Ahn JM, Song H, et al: Comprehensive intravascular ultrasound assessment of stent area and its impact on restenosis and adverse cardiac events in 403 patients with unprotected left main disease. *Circ Cardiovasc Interv.* 2011;4:562-569.)

DISEASE LOCATION: OSTIAL OR MIDSHAFT VERSUS DISTAL LEFT MAIN CORONARY ARTERY

Percutaneous coronary intervention of the distal LM bifurcation has been associated with higher follow-up MACE rates than PCI limited to the LM ostium or midshaft in most, but not all, studies. The DELTA (Drug-Eluting Stent for Left Main Coronary Artery Disease) registry is the largest study to examine this issue.¹¹⁷ A total of 1612 patients with LM PCI were included in the study, including 1130 patients with distal bifurcation lesions. During a median follow-up of 3.4 years, patients with distal bifurcation disease had a greater rate of MACE (a composite endpoint of death, MI, or TVR) compared with ostial or midshaft lesions (propensity-score adjusted HR, 1.48; 95% CI, 1.16–1.89; $P = .001$), primarily driven by a higher rate of TVR (propensity-score adjusted HR, 1.68; 95% CI, 1.19–2.38; $P = .003$). Similar findings have been reported by other groups.⁹⁹

In another registry analysis of 1111 patients with 2 years of follow-up, Palmerini et al.¹¹⁸ showed that distal bifurcation lesions had a lower freedom from MACE compared with ostial or midshaft lesions (72% vs 80%; $P = .03$); however, whereas patients with distal bifurcation lesions treated with a two-stent strategy had worse outcomes, patients with distal bifurcation lesions treated with a one-stent (provisional) approach had clinical outcomes similar to those with ostial and midshaft LM lesions.

ONE- VERSUS TWO-STENT APPROACH FOR LEFT MAIN CORONARY ARTERY BIFURCATION DISEASE

Bifurcation lesions represent more than 50% of all LM PCIs.²⁹ True distal bifurcation lesions may be treated by either a one- or two-stent strategy. Choice of strategy is based on vessel and lesion characteristics (plaque distribution, diameter of the branches and the angle between them, anatomy of the SB) in addition to operator experience and expertise.

Few dedicated RCTs have compared stenting strategies in LM bifurcation lesions. Most bifurcation studies have been performed in populations that include both non-LM and LM bifurcation, with the latter usually representing only 2% to 10% of all bifurcation lesions. Nevertheless, outcomes from these studies may be extrapolated to LM patients, although the results of adverse outcomes can be more severe in the LM cohort. Nearly all RCTs in non-LM bifurcations have demonstrated that a routine two-stent approach (stenting both the MV and SB) offers no angiographic or clinical benefits compared with a provisional stenting strategy (stenting the MV only, with stenting of the SB reserved for suboptimal balloon angioplasty results).¹¹⁹⁻¹²⁴ One trial did report lower rates of angiographic and clinical restenosis with a routine two-stent approach,¹²⁵ whereas another trial demonstrated an increase in adverse ischemic events, mainly periprocedural MI, with the two-stent approach.¹²⁶ All of these studies were limited by modest sample size, heterogeneity in SB lesion severity and length, and diversity in the two-stent technique. From a registry report of 782 LM bifurcation patients undergoing PCI with DES, provisional



stenting resulted in significantly higher MACE-free survival at 2-year follow-up compared with a routine two-stent approach (75% vs 67%; $P = .02$). The lower MACE in the provisional group was primarily driven by a greater TLR-free survival rate (87% vs 73%; $P = .00001$).¹¹⁸

Two RCTs evaluated the role of a routine two-stent approach vs provisional stenting specifically in LM PCI, the DKCRUSH-V (Double Kissing and Double Crush Versus Provisional T Stenting Technique for the Treatment of Unprotected Distal Left Main True Bifurcation Lesions: A Randomized, International, Multi-Center Clinical) trial⁹¹ and the EBC MAIN (European bifurcation club Left Main Coronary Stent study: a randomized comparison of stepwise provisional vs systematic dual stenting strategies) study.¹²⁷ The DKCRUSH-V trial sought to determine whether a planned double-kissing crush (DK) two-stent technique was superior to provisional stenting for patients with true distal LM bifurcation lesions. A total of 482 patients with true distal LM bifurcation lesions (Medina 1, 1, 1 or 0, 1, 1) were randomized to provisional stenting ($n = 242$) or DK stenting ($n = 240$).⁹¹ The primary endpoint was the 1-year composite rate of target lesion failure (TLF): cardiac death, target vessel MI, or clinically driven TLR. Routine 13-month angiographic follow-up was scheduled after ascertainment of the primary endpoint. TLF within 1 year occurred in 26 patients (10.7%) assigned to provisional stenting and in 12 patients (5.0%) assigned to DK (HR, 0.42; 95% CI, 0.21–0.85; $P = .02$). Compared with provisional stenting, DK also resulted in lower rates of target vessel MI (2.9% vs 0.4%; $P = .03$) and definite or probable stent thrombosis (3.3% vs 0.4%; $P = .02$). Clinically driven TLR (7.9% vs 3.8%; $P = .06$) and angiographic restenosis within the LM complex (14.6% vs 7.1%; $P = .10$) also tended to be less frequent with DK than with provisional stenting. There was no significant difference in cardiac death between the groups. There were no significant interactions between any of the subgroups and technique randomization for the 1-year relative rates of TLF, although the absolute reduction in TLF was greater in complex compared with simple distal LM bifurcation lesions.

In contrast, the EBC-MAIN demonstrated that among patients with true bifurcation LM stenosis requiring intervention, fewer major adverse cardiac events occurred with a stepwise layered provisional approach than with planned dual stenting, although the difference was not statistically significant.¹²⁷ A total of 467 patients with true LM bifurcation lesions requiring intervention were enrolled. Patients were randomly allocated to a stepwise layered provisional strategy ($n = 230$) or a systematic dual-stent approach ($n = 237$). The primary endpoint (a composite of death, MI, and TLR at 12 months) occurred in 14.7% of the stepwise provisional group versus 17.7% of the systematic dual-stent group (HR, 0.8; 95% CI, 0.5–1.3; $P = .34$). Secondary endpoints were death (3.0% vs 4.2%; $P = .48$), MI (10.0% vs 10.1%; $P = .91$), TLR (6.1% vs 9.3%; $P = .16$), and stent thrombosis (1.7% vs 1.3%; $P = .90$). Procedure time, x-ray dose, and consumables favored the stepwise provisional approach. Symptomatic improvement was excellent and equal in each group. In light of those findings, the authors concluded that the stepwise provisional strategy should remain the default for distal LM stem bifurcation intervention.

Similarly, among patients with distal LM bifurcation disease in the EXCEL trial randomized to PCI, 3-year adverse outcomes were worse with planned two-stent treatment compared with a provisional one-stent approach, a difference that was confined to patients without major involvement of both LM SB vessels.¹²⁸ Among 529 patients undergoing planned distal LM PCI, 344 (65.0%) and 185 (35.0%) were treated with intended one-stent provisional and planned two-stent techniques, respectively. The primary composite endpoint rate of death, MI, or stroke at 3 years was significantly lower in patients treated with the provisional one-stent versus planned two-stent method (14.1% vs 20.7%; adjusted HR, 0.55; 95% CI, 0.35–0.88; $P = .01$), driven by differences in cardiovascular death (3.3% vs 8.3%; $P = .01$) and MI (7.7% vs 12.8%; $P = .06$). The 3-year rate of ischemia-driven revascularization of the LM complex was also lower in the provisional group (7.2% vs 16.3%; $P = .001$). In 342 patients with distal LM bifurcation disease that did not involve both major SB vessels, the 3-year primary endpoint was lower with a provisional one-stent vs planned two-stent technique (13.8% vs 23.3%; $P = .04$), whereas no significant difference was present in 182 patients with distal LM bifurcation disease that did involve both SB vessels (14.3% vs 19.2%; $P = .36$).

Finally, a recent meta-analysis of all RCTs evaluating the two-stent strategy versus provisional stenting among bifurcation lesions demonstrated that provisional single-stent strategy was associated with a reduction in all-cause mortality at long-term follow-up. Indeed, a pooled analysis of 9 RCTs including 3265 patients with reported mean weighted follow-up of 3.1 ± 1.8 years. Provisional single stenting was associated with lower all-cause mortality (2.94% vs 4.23%; risk ratio [RR], 0.69; 95% CI, 0.48–1.00; $P = .049$). There was no difference in major adverse cardiac events (15.8% vs 15.4%; $P = .79$), MI (4.8% vs 5.5%; $P = .51$), TLR (9.3% vs 7.6%; $P = .19$), or stent thrombosis (1.8% vs 1.6%; $P = .28$) between the groups. Pre-specified sensitivity analysis of long-term mortality at a mean of 4.7 years of follow-up showed that the provisional single-stent strategy was associated with reduced all-cause mortality (3.9% vs 6.2%; RR, 0.63; 95% CI, 0.42–0.97; $P = .036$).

Thus, most experts agree that the provisional approach should be the default LM bifurcation treatment strategy for most cases.^{129,130} Exceptions include more complex anatomy with severe disease in both the LAD and LCX, with SB lesions larger than 10 mm, or when a sharply angulated SB entry is present. This was shown in the Two-stent vs Provisional Stenting Techniques for Patients With Complex Coronary Bifurcation Lesions (DEFINITION-II) trial ($n = 653$), in which an upfront two-stent DK technique for patients with complex bifurcation lesions with a long (>10 mm) diseased SB had significant improvement in clinical outcomes (1-year TLF 11.4% vs 6.1%; $P = .019$) compared with the provisional approach.¹³¹

TWO-STENT TECHNIQUES

Although many techniques have been described for a two-stent approach (a comprehensive description of which is

beyond the scope of this chapter), only a few have been compared in RCTs. The Nordic Stent Technique Study randomized 424 patients undergoing PCI for bifurcation lesions to either the crush or culotte technique.¹³² Only 10% were LM bifurcation lesions. The primary outcome was MACE, a composite of cardiac death, MI, TVR, or stent thrombosis. At 6 months, there was no significant difference between the 2 groups (4.3% for crush vs 3.7% for culotte; $P = .87$); however, the rate of procedure-related increase in biomarkers of myocardial injury was 15.5% with the crush technique versus 8.8% with the culotte ($P = .08$). At 8 months, there was a trend toward less in-segment restenosis (12.1% vs 6.6%; $P = .10$) and significantly reduced ISR (10.5% vs 4.5%; $P = .046$) after culotte stenting.

In the dedicated LM bifurcation two-stent technique trial, the DKCRUSH III (DK Crush Versus Culotte Stenting for the Treatment of Unprotected Distal Left Main Bifurcation Lesions) study compared the DK technique vs culotte stenting among 450 unprotected LM patients.¹³³ The culotte group had a significantly greater 12-month MACE rate (the primary endpoint) compared with the DK group (16.3% vs 6.6%; $P = .001$), which was mainly driven by increased TVR (11.0% vs 4.3%; $P = .016$). Notably, SB ISR was also significantly higher in the culotte group compared with the DK group (12.6% vs 6.8%; $P = .037$). The DK group compared with the culotte group also had lower MACE rates among patients with bifurcation angle greater than 70 degrees (3.8% vs 16.5%; $P < .001$) and patients with SYNTAX scores of 23 or greater (7.1% vs 18.9%; $P = .006$); however, highly angulated bifurcation lesions may be most optimally (and simply) treated with a modified T-stent or T-stenting and small protrusion (TAP) technique, which was not tested in this study. However, in a post hoc analysis of the ISAR-Left Main study, culotte stenting had lower rates of 6- to 9-month ISR (21% vs 56%; $P = .02$) and 1-year TLR (15% vs 56%; $P < .001$) than T-stenting, although routine angiographic follow-up complicates interpretation of these results.⁹⁹

DEDICATED BIFURCATION STENTS

Patients in whom a two-stent approach is planned may be candidates for dedicated bifurcation stents. In the TRYTON randomized trial in non-LM bifurcation lesions, the bare-metal Tryton Side Branch Stent (Tryton Medical), which facilitates culotte stenting, compared with a provisional approach did not meet the 9-month primary noninferiority endpoint, a composite of cardiac death, target vessel MI, and target vessel failure (12.9% with a provisional approach vs 17.4% with the Tryton; $P = .11$) mainly because of a higher rate of periprocedural MI (13.6% vs 10.1%; $P = .19$)¹³⁴; however, the trial did meet the 9-month angiographic secondary superiority endpoint of reduced SB percent diameter stenosis (38.6% with a provisional approach vs 31.6% with the Tryton; $P = .002$). These findings highlight that SB angiographic restenosis, especially in smaller SBs, is uncommonly expressed clinically. Use of the Tryton for true bifurcation lesions involving the LM has been described and appears to be safe.^{135,136} That

being said, the Tryton stent is no longer commercially available. There are other dedicated bifurcation stents in various stages of evaluation, including the Nile PAX (Minvasys SAS) and AXCESS-LMTM (Biosensors) stents.^{137,138} Additional studies are required to examine the potential role of dedicated bifurcation stents in LM (and non-LM) disease.

IMPORTANCE OF FINAL PROXIMAL OPTIMIZATION TECHNIQUE AND SELECTIVE KISSING BALLOON INFLATION

Although final kissing balloon was previously considered as a mandatory step when using a two-stent strategy,^{139,140} it is still a matter of debate whether routine kissing should be systematically performed with provisional stenting, especially when a satisfactory final result in the SB is achieved.¹²⁷ Recently, bifurcation experts recommend a provisional stenting approach as the default strategy for most bifurcation lesions, with a systematic postdilation of the proximal segment of the main branch, called proximal optimization technique (POT). If a satisfactory result is achieved with no-flow or angiographic compromise in the SB, kissing could be avoided.^{130,141} The Nordic Bifurcation Study III (NORDIC III) trial compared a routine strategy of final kissing with no final kissing in patients undergoing a provisional stenting approach. Despite a reduction in angiographic SB restenosis at 8-month follow-up in true (non-LM) bifurcations, no differences in clinical endpoints were apparent (6-month MACE, 2.1% vs 2.5%; $P = 1.00$), and procedural duration, contrast use, and fluoroscopy times were greater with final kissing balloon inflations.¹⁴²

ROLE OF IMAGING

Angiography

Although angiography has long been considered the gold standard for coronary evaluation, important limitations that are relevant to LM evaluation and revascularization have been described. Angiographic assessment of lesion severity involving the LM is often challenging, in part because the detection of diffuse, concentric disease in the LM is difficult because of the lack of a nondiseased reference segment for comparison. Moreover, vessel overlap, ostial angulation and deformity, foreshortening, and streaming of contrast medium from the catheter tip make accurate assessment of the LM segment notoriously difficult even by the most experienced clinicians (Figure 8.5). Studies have shown significant mismatch between angiography and both IVUS⁵⁴ and fractional flow reserve (FFR),¹⁴³ particularly in angiographically intermediate lesions. Therefore, the final decision regarding whether to revascularize intermediate LM lesions should not be based on coronary angiography alone. Adequate knowledge of the strengths and weaknesses of IVUS and FFR are mandatory for proper LM assessment. Additional evaluation with IVUS/FFR may avoid revascularization of functionally insignificant lesions and the associated complications and costs.

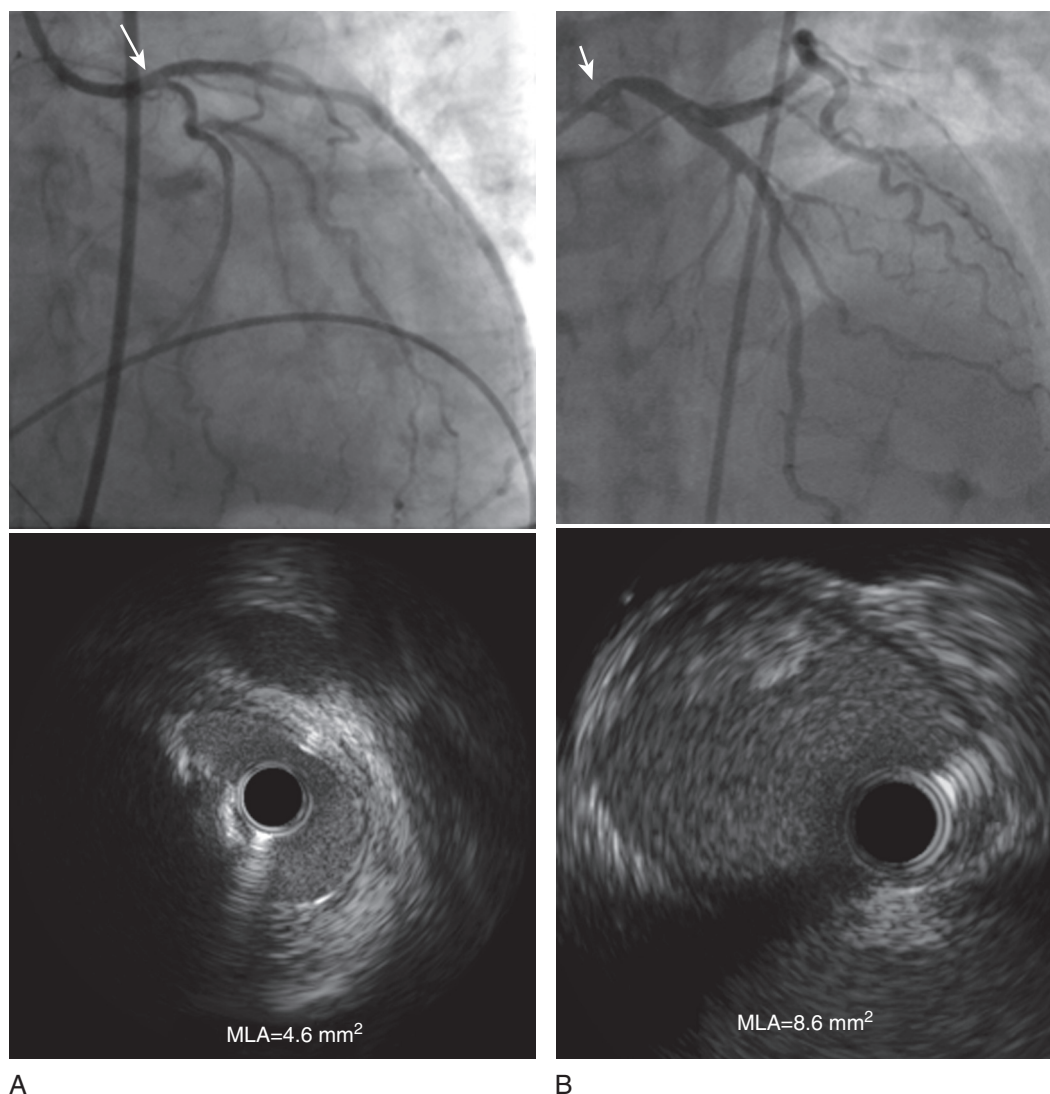


FIGURE 8.5 Discrepancy between angiography and intravascular ultrasonography (IVUS). **A**, Coronary angiogram showing haziness in the shaft of the left main coronary artery, with no obvious stenosis. IVUS assessment demonstrated a significant stenosis (minimum lumen area [MLA], 4.6 mm²). **B**, Coronary angiogram showing a potential ostial lesion. IVUS assessment demonstrated the absence of a significant lesion (MLA 8.6 mm²). (Courtesy of Akiko Maehara.)

Intravascular Ultrasonography

Intravascular ultrasonography has an important role both before and after PCI of LM lesions. Before PCI, IVUS may be used to objectively assess stenosis severity, lesion extent (including SB involvement), lumen dimensions, plaque distribution, and calcification. Abizaid et al.¹⁴⁴ were among the first to highlight the important lack of correlation between angiographic and IVUS assessment of lesion severity. They also demonstrated the importance of the minimal lumen diameter (MLD) in prediction of future ischemic adverse events. Jasti et al.⁵⁵ identified an LM MLD smaller than 2.8 mm and a minimum lumen area (MLA) smaller than 5.9 mm² as being the most predictive of an FFR value less than 0.75. In a patient cohort with a smaller body surface area, Kang et al.⁵⁶ reported that the only independent predictor of FFR less than 0.80 was the LM MLA value on IVUS, with a value less than 4.8 mm² being the most accurate correlate. A larger cohort subsequently confirmed this finding, with an IVUS-derived MLA of smaller than 4.5 mm² representing a useful index of an FFR of less than

0.80 in patients with isolated ostial and shaft intermediate LMCA stenosis.⁵⁷

Subsequent studies have attempted to identify an IVUS MLA cutoff to safely guide the LM revascularization decision-making process. Spanish Working Group on Interventional Cardiology (LITRO) was a multicenter prospective study validating the IVUS-derived cutoff value of 6 mm² as a safe MLA parameter to guide revascularization of intermediate LM lesions.⁵⁴ A total of 354 patients were enrolled, among whom 179 with an LM MLA of 6 mm² or greater were treated medically and 152 with an LM MLA less than 6 mm² were revascularized (45% with PCI and 55% with CABG). No difference in the 2-year rate of cardiac death and MI was observed between the 2 groups. Although the 6 mm² MLA value is widely accepted as the IVUS threshold at which revascularization may be safely deferred, the optimal LM MLA cutoff still remains a matter of debate,⁵⁸ with the 4.8-mm² value also shown as having clinical utility in an Asian cohort.⁵⁶

In addition to assessing intermediate lesions, IVUS plays an important role in interventional guidance of LM



procedures, including choice of stent diameter and length, need for debulking, and technique selection (e.g., provisional vs planned two-stent approach). After LM stenting, IVUS is useful in assessing plaque vs carinal shift, geometric changes in the POC, and optimization of MLA (stent expansion).¹⁴⁵ Suboptimal stent expansion is the single most important factor that has most strongly been associated with stent thrombosis and restenosis after LM PCI.¹¹⁶ Stent underexpansion is more common with a two-stent approach, particularly at the ostium of the LCX, partially explaining the higher rates of ISR in this location. The proposed minimal stent area (MSA) cutoff values are shown in Figure 8.4, although as a general rule, the larger the MSA, the lower the adverse event rates. Kang et al.¹¹⁶ have evaluated the optimal IVUS stent area to predict angiographic ISR after SES implantation for LM disease. The MSA values post-PCI that best predicted ISR on a segmental basis were 8.2 mm² for the LM shaft, 7.2 mm² for the POC, 6.3 mm² for the ostial LAD, and 5.0 mm² for the ostial LCX (or 4.0 mm² if the ostial LCX was not stented). Stent underexpansion at any of these locations was an independent predictor for 2-year MACE, especially repeat revascularization, but stent malapposition did not predict ISR or MACE.

Park et al.⁹⁰ have reported that long-term mortality in patients undergoing IVUS-guided LM stenting may be lower than in those undergoing LM stenting with angiographic guidance alone. Similarly, among 2468 patients from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry), patients who underwent unprotected LM PCI guided by IVUS demonstrated improved outcomes compared to angiography-guided PCI only.⁵⁹ IVUS was associated with larger stent diameters (median, 4 mm vs 3.5 mm) and was associated with significantly lower occurrence of the primary composite endpoint of all-cause mortality, restenosis, or definite stent thrombosis (HR, 0.65; 95% CI, 0.50–0.84) and all-cause mortality alone (HR, 0.62; 95% CI, 0.47–0.82). In 340 propensity score-matched pairs, IVUS was also associated with significantly lower occurrence of the primary endpoint (HR, 0.54; 95% CI, 0.37–0.80). Kinnaird et al.¹⁴⁶ also demonstrated a benefit of mortality among 5056 pairs of propensity-matched patients undergoing IVUS PCI vs angiography-guided PCI for unprotected LM PCI. A lower rate of coronary complications, lower in-hospital major adverse cardiac events (OR, 0.470; 95% CI, 0.37–0.590; $P < .001$), and improved 30-day mortality (OR, 0.540; 95% CI, 0.430–0.680; $P < .001$) and 12-month mortality (OR, 0.660; 95% CI, 0.570–0.770; $P < .001$) rates were observed with imaging use compared with no imaging use. Greater mortality reductions were observed with higher operator LM PCI volume. In logistic regression modeling, imaging use was associated with improved 12-month survival.

In the EXCEL trial, 290 of the 948 patients randomized to PCI had both pre- and post-PCI IVUS.¹⁴⁷ However, IVUS guidance was used in 722 of the 948 patients at some stage of the procedure, and it was strongly recommended to optimize stenting. In a substudy of these 722 patients, it was found that a small final MSA, measured by IVUS after LMS PCI, was associated with adverse events (including death, MI, and stent thrombosis) during long-term follow-up.

Three MSA tertiles were assessed as small (4.4–8.7 mm²), intermediate (8.8–10.9 mm²), and large (11–17.8 mm²), with a primary endpoint of all-cause mortality, MI, or stroke. A graded relationship was found between MSA tertiles with an improved primary endpoint and increasing MSA size (19.4%, $n = 32$ or 172 in the smallest tertile; 16.1%, $n = 26$ or 169 in the intermediate tertile; and 9.6%, $n = 15$ or 163) in the largest tertile; $P = .01$ for smallest versus largest tertile). A substudy in the NOBLE trial also demonstrated a significant reduction in TLR (5.1% vs 11.6%, $P = .01$) with IVUS-guided stent optimization for LMS PCI, but no difference in MACCE was found.⁶⁰

Optical Coherence Tomography

Finally, optical coherence tomography (OCT) is an intracoronary imaging modality with higher resolution than IVUS and offers a more detailed assessment of the lumen and intima. Drawbacks of OCT for LM assessment include its reduced depth of penetration compared with IVUS, challenged with ostial lesion, and difficulty in clearing the LM lumen with an adequate flush. Although interesting observations have recently been presented regarding OCT optimization of bifurcation LM PCI,^{148–152} further data are needed before this technique can be widely recommended to guide LM decision making.

FRACTIONAL FLOW RESERVE

Pressure wire-derived FFR is the gold standard for the physiological assessment of coronary artery stenosis,^{14,15,153–156} and it may be useful in the management of bifurcation lesions.^{157,158} Data from the randomized Deferral of Percutaneous Coronary Intervention (DEFER), Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME I), and FAME II trials in non-LM CAD have demonstrated that an FFR-guided revascularization strategy is associated with improved outcomes compared with a purely angiographic strategy when managing single-vessel or multivessel CAD.^{153,154,156} Subsequently, several investigators have demonstrated the potential utility of pressure wire assessment in the assessment of LM lesions with PCI.^{55,143,159–164}

Hamilos and colleagues¹⁴³ evaluated the long-term clinical outcomes of an LM revascularization strategy based on FFR in 215 patients with angiographically indeterminate LM coronary artery stenosis. Patients with FFR of 0.80 or greater were treated medically (nonsurgical group; $n = 138$), and patients with FFR below 0.80 were treated with CABG (surgical group; $n = 75$). The 5-year survival estimates were similar in both groups (89.8% in the nonsurgical group and 85.4% in the surgical group; $P = .48$). The 5-year event-free survival (a composite of death, MI, or revascularization) estimates were 74.2% and 82.8% in the nonsurgical and surgical groups, respectively ($P = .50$). In 23% of patients with a diameter stenosis less than 50%, the LM coronary artery stenosis was hemodynamically significant by FFR. This study illustrates the value of an FFR-guided strategy when the severity of the LM stenosis is uncertain by angiography.



Although FFR is useful to assess the physiologic significance of the isolated LM lesion, several theoretical limitations of FFR in patients with LM plus concomitant multivessel CAD should be appreciated. Because FFR readings across the LM segment may be influenced by the presence of disease within any of the distal coronary segments, high-grade stenoses within the LAD or LCX territories may artificially increase the FFR measured across the LM if the transducer is placed distally.¹⁶⁴ In this situation, an FFR pullback should be undertaken starting within both daughter branches to localize the most significant distribution of disease across the region bordering the distal LM segment and ostia of both daughter branches.^{165,165} Alternatively, FFR across the LM segment may be artificially low in the setting of severe downstream disease if the transducer is placed in a branch without severe disease. PCI of functionally significant distal lesions may be required to unmask the true hemodynamic significance of the diseased LM segment. FFR may also be useful in determining the functional significance of an angiographically narrowed LCX ostium after provisional stenting, specifically when ostial stenosis is larger than 75%.¹⁵⁷

Other issues to consider when using FFR to assess intermediate LM lesions are as follows:

1. There is no definite consensus related to the exact FFR cutoff for LM. Although an FFR of 0.80 or less is usually considered appropriate to initiate revascularization, some argue that an FFR value between 0.80 and 0.85 should be repeated and complemented with an IVUS assessment.
2. Special attention should be deployed to avoid deep engagement of the guiding catheter (pressure damping) while performing the FFR measurement, which may falsely increase the FFR value.
3. Given the large myocardium mass served by the LM, adenosine doses should be increased to ensure maximal hyperemia if the FFR is borderline (e.g., <0.85 but >0.80).

In summary, improvement in procedural and clinical outcomes with the use IVUS- and FFR-guided LM PCI have been demonstrated in several moderate-sized nonrandomized studies. Nevertheless, given the potential dramatic clinical consequences of stent failure (thrombosis or restenosis) within the LM segment, IVUS or FFR guidance is strongly recommended during LM PCI to optimize acute and long-term outcomes.

MYOCARDIAL INFARCTION CAUSED BY LEFT MAIN CORONARY ARTERY THROMBOSIS

Most LM revascularization studies have excluded patients presenting with ST-segment elevation MI (STEMI). Although primary PCI is the preferred revascularization strategy in patients with STEMI, limited data are available in those presenting with LM thrombosis. In a meta-analysis including a total of 977 patients, 26% of patients presenting to a hospital with STEMI involving the LM were in cardiogenic shock; these patients had significantly higher 30-day all-cause mortality rate compared with those presenting without

shock (55% vs 15%; $P < .001$).¹⁶⁶ Similarly, in the Acute Myocardial Infarction in Switzerland (AMIS) Plus Registry, in which 348 patients undergoing LM primary PCI were compared with 6318 patients undergoing primary PCI of a non-LM vessel, LM patients presented more frequently with cardiogenic shock (12.2% vs 3.5%; $P = .001$) and had higher mortality rates, especially when concomitant non-LM CAD were present.¹⁶⁷ Finally, using the British Cardiovascular Intervention Society database, Patel and colleagues¹⁶⁸ compared the 3-year clinical outcomes of 568 patients presenting with STEMI with unprotected occlusive LM (Thrombolysis in Myocardial Infarction [TIMI] flow grade 0/1 and diameter stenosis >75%) with 1045 emergency patients treated with nonocclusive LM disease. Compared with nonocclusive LM disease, occlusive LM disease in patients with STEMI was associated with a doubling in the likelihood of periprocedural shock (57.9% vs 27.9%; $P < .001$) or intraaortic balloon pump support (52.5% vs 27.2%; $P < .001$). In-hospital (43.3% vs 20.6%; $P < .001$), 1-year (52.8% vs 32.4%; $P < .001$), and 3-year (73.9% vs 52.3%; $P < .001$) mortality rates were also markedly higher in patients with occlusive LM disease.

HEMODYNAMIC SUPPORT

The routine use of hemodynamic support devices such as intraaortic balloon counterpulsation or left ventricular support (e.g., microaxial propelling pump) has been advocated in specific patients undergoing LM PCI to reduce periprocedural risks.¹⁶⁹⁻¹⁷² The PROTECT (Impella-Supported PCI in High-Risk Patients With Complex Coronary Artery Disease and Reduced Left Ventricular Function) II trial, in which 452 high-risk patients undergoing PCI were randomized to hemodynamic support with the Impella 2.5 versus intraaortic balloon counterpulsation, failed to demonstrate reductions in mortality rate or adverse events at 30 and 90 days.⁷⁶ Among 107 patients undergoing PCI for unprotected LM disease, the relative risks for major adverse events at 30 days (RR, 1.02; 95% CI, 0.65–1.60) and 90 days (RR, 0.88; 95% CI, 0.59–1.33) were also nonsignificantly different with the two support devices. Although it is generally accepted that routine use of hemodynamic support devices in LM PCI is not required, the use of such devices to decrease procedural risk may be reasonable in some clinical situations (Table 8.7). The ongoing PROTECT 4 trial (NCT04763200) will help to better understand the role of mechanical support device in high-risk patients such as LM PCI.

TABLE 8.7 Clinical Scenarios in Which Hemodynamic Support May Be Beneficial During Left Main Coronary Artery Percutaneous Coronary Intervention

- Cardiogenic shock
- Refractory or decompensated heart failure
- Low left ventricular ejection fraction (<40%)
- Concomitant critical disease of the right coronary artery
- Severe multivessel disease
- Use of rotational atherectomy
- High thrombotic burden or otherwise at high risk for no or slow re-flow phenomenon
- Left dominance

DUAL ANTIPLATELET THERAPY SELECTION AND DURATION

Left main coronary artery PCI is one of the most complex lesion subsets, involving a large area of myocardium. Stent thrombosis is usually catastrophic, and a strategy to avoid thrombotic events could lead to improved clinical outcomes. Recently, growing evidence suggests that more potent or longer DAPT could be beneficial in the setting of complex PCI, including LM PCI and bifurcations,¹⁷³⁻¹⁷⁸ and that early discontinuation of DAPT (<3 months) could be potentially detrimental in patients with such complex disease.^{179,180} Data from registries involving 1142 patients undergoing LM PCI demonstrated that a strategy of DAPT longer than 12 months compared to less than 12 months resulted in a lower rate of cardiac death, stroke, MI, and stent thrombosis up to 5 years of follow-up (2.3% vs 5.4%, adjusted HR, 0.37; 95% CI, 0.19–0.71; $P = .003$).¹⁸¹ Similarly, a large series demonstrated that among 3865 patients free of ischemic and bleeding events at 12 months, 1727 (44.7%) remained on DAPT (mostly clopidogrel based [97.7%]) beyond 12 months after LM PCI. DAPT for longer than 12 months versus less than 12 months was associated with a significantly reduced risk of the 3-year primary outcome of death, stroke, MI, or stent thrombosis (2.6% vs 4.6%; adjusted HR, 0.59; 95% CI, 0.41–0.84). Bleeding events (Bleeding Academic Research Consortium [BARC] 2-3-5) were not significantly different between the two strategies (1.8% vs 1.6%; adjusted HR, 1.07; 95% CI, 0.65–1.74¹⁸²); however, these two series are in contrast with a subanalysis of the EXCEL trial that showed no benefit to continued DAPT beyond 1 year.¹⁸³ More important, a nontrivial proportion of patients undergoing LM PCI outside large randomized are at high risk of bleeding, and benefits of prolonged DAPT for thrombotic events prevention have to be balanced against the risk of bleeding events. A recent series of real-world LM PCI demonstrated that among 619 patients undergoing unprotected LM PCI, 55.3% were identified as being at high risk for bleeding. The rate of death, MI, or stroke at 12 months was fourfold higher in patients at high bleeding risk compared with those without high bleeding risk (20.5% vs 4.9%; HR, 4.43; 95% CI, 2.31–8.48), driven by an increased risk for all-cause death (HR, 3.88; 95% CI, 1.88–8.02) and MI (HR, 6.18; 95% CI, 1.83–20.9). Rates of TVR or TLR and stent thrombosis were comparable in the two groups. Bleeding occurred more frequently in patients at high risk of bleeding (HR, 3.77; 95% CI, 1.83–7.76).¹⁸⁴

In the SYNTAX trial, stent thrombosis with TAXUS paclitaxel eluting-stent (TAXUS PES) occurred in about 10% of patients at 5 years, significantly contributing to MACE among the randomized PCI cohort.¹⁸⁵ Of note, 19.4% of all stent thromboses in SYNTAX occurred in the LM segment. Premature discontinuation of DAPT is an important predictor of stent thrombosis.¹⁸⁶ Most of the episodes of death or MI occurred among patients treated with DAPT for less than 6 months in the Gruppo Italiano Studi Emodinamici (GISE) survey, especially in the setting of an acute coronary syndrome.¹⁸⁷ Given the potential dramatic consequences of DAPT discontinuation after LM PCI, every effort should be made to ensure patient medication compliance. Despite the newer generation of DES showing an improved safety

profile,¹¹² the optimal duration of DAPT after PCI using DES placement still remains a matter of active debate.¹⁸⁸⁻¹⁹⁰ In the absence of compelling data, it seems reasonable to recommend DAPT for at least 1 year after LM PCI.^{14,15}

Migliorini et al.¹⁹¹ showed that in patients who underwent LM PCI, high residual platelet reactivity after a loading dose of 600 mg of clopidogrel was associated with a fourfold increase in the risk of stent thrombosis and cardiac death. High residual platelet reactivity was the only independent predictor of both stent thrombosis and cardiac death in this study. The more potent P₂Y₁₂ inhibitors ticagrelor and prasugrel have been shown to reduce stent thrombosis in a large cross section of patients with acute coronary syndromes undergoing PCI,^{192,193} although few patients in these studies had LM disease. Although there are no conclusive studies to date demonstrating the utility of ticagrelor or prasugrel in patients with LM disease, the use of these agents may be reasonable in such patients who are at high risk of thrombosis (e.g., suboptimal two-stent bifurcation treatment of multiple stents for complex CAD) and low risk of bleeding.

FOLLOW-UP AFTER LEFT MAIN CORONARY ARTERY PERCUTANEOUS CORONARY INTERVENTION

According to the most recent 2021 ACC/AHA guideline, routine angiographic follow-up is not recommended after unprotected LM PCI.¹⁴ In contrast, the 2018 ESC/EACTS guidelines recommend that after high-risk PCI (e.g., unprotected LM stenosis), late (3–12 months) surveillance angiography may be considered, irrespective of symptoms (Class IIB, LOE B).¹⁵ The role of routine or selective computed tomography (with or without physiological assessment) after LM PCI remains to be defined.

LEFT MAIN CORONARY ARTERY BIFURCATION PCI TECHNIQUES

Distal bifurcation lesions involving only one SB should usually be approached with a provisional technique (planned one stent with or without SB balloon angioplasty and with or without final kissing). For true bifurcations involving the distal LM bifurcation and the need for a two-stent approach, a variety of techniques have been described. With this approach, a POT and potentially final kissing balloon inflation are mandatory to optimize long-term outcomes and preserve future accessibility to the SBs. The choice of the most appropriate two-stent LM PCI technique varies according to factors such as plaque distribution (Medina classification), lesion location (ostium, midshaft, or distal involving bifurcation), LM bifurcation angulation, and operator experience and expertise.

PROVISIONAL STENT TECHNIQUE

The provisional stent technique involves the initial placement of a single stent in the LM and LAD (or rarely the LCX)



with crossover of the other SB (Figure 8.6 and Video 8.1).

The steps are as follows:

1. Wiring the MV and SB
2. Balloon predilation of the MV and SB (SB optional)
3. Stenting MV with both wires in place
4. Assessment of SB integrity: Consider whether balloon angioplasty or stenting is required. If the stenosis is less than 50%, without good flow and without dissection, SB treatment may be deferred. Otherwise, intervention is usually performed, most frequently balloon angioplasty first to achieve an acceptable result. Stenting may be required in about 20% of cases (although the threshold varies by operator from <10% to >30%) if TIMI flow is

less than 3; there is severe ostial compromise (>80% stenosis), threatened SB closure, or dissection type B or greater; or FFR is less than 0.75. Placement of a second stent in the SB may be done by T-stent, TAP, reverse crush, or culotte approach.

5. Rewiring the SB and final kissing balloon inflation (per operator discretion if an SB stent is not placed; mandatory if two-stent approach).

Positioning of a wire in the SB until MV stenting or post-dilation is complete, especially in the presence of complex anatomy (tortuosity, acute angle, severe stenosis, presence of heavy calcification), is an important step and facilitates SB access in case of SB closure or significant

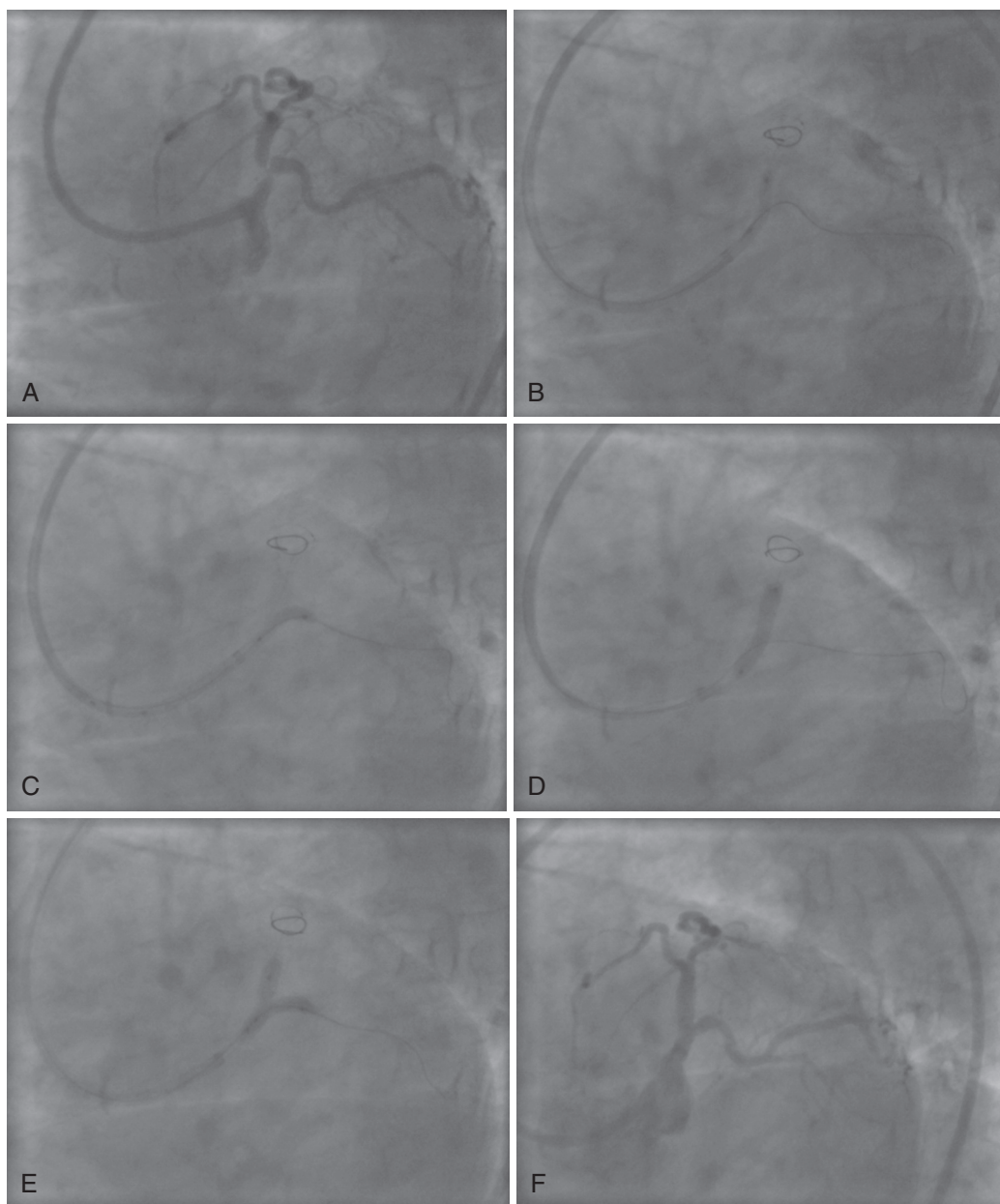


FIGURE 8.6 Left main coronary artery (LM) percutaneous coronary intervention using a one-stent provisional approach with final kissing (see also Video 8.1). **A**, Baseline angiogram showing severe distal LM disease with involvement of the proximal left anterior descending coronary artery (LAD) and an intermediate lesion of the left circumflex (LCX). **B**, Predilation of the LM and LAD. **C**, Predilation of the LCX. **D**, Stent implantation in the LM–LAD axis. **E**, After removal and rewiring of the LCX, simultaneous final kissing. **F**, Final angiogram showing an excellent result.



compromise. The temporary jailed wire can usually be retrieved easily. A jacketed polymer-coated wire should not be used for this purpose, however, because the polymer may be stripped off during retrieval of the jailed wire. Polymer-coated wires may be used effectively, however, for recrossing the stent into the SB. Postdilation of the proximal MV stent after LM stent implantation before kissing balloon inflation or placement of a second stent (POT) is strongly recommended to optimize final geometry of the bifurcation and facilitate SB accessibility through the distal side cell of the MV stent.^{127,194}

TWO-STENT TECHNIQUES

Various two-stent techniques have been described. Selection of a particular technique should be based on bifurcation characteristics, operator preference, and experience. The following general principles should be considered when selecting the most appropriate technique for a given patient:

1. Size of SB: In LM PCI, the SB, which is most frequently the LCX artery, may supply a relatively large amount of myocardium (especially in case of left dominance). Preserving its patency and integrity is important. If a significant discrepancy in vessel diameter exists between the SB and the LM body (ie, SB considerably smaller than MV), the culotte stenting technique may be problematic and should be avoided. T-stenting, the crush technique, or a DK crush technique should be favored in this situation.
2. Lesion length in SB: Focal lesions smaller than 5 mm, even if angiographically severe, are rarely physiologically significant. They should usually be treated initially with a provisional approach followed by FFR-guided assessment and management and optimized with or without final kissing inflation. However, if a significant lesion extends several millimeters (>5 mm) into the SB, especially if angulated or calcified, a two-stent approach should be considered.
3. Bifurcation angulation: For angles less than 70 degrees or with Y-shaped morphology, SB access may be more easily performed; however, plaque shift (or carina shift) may still occur and be severe. In lesions with angles 70 degrees or greater or with T-shaped morphology, SB access is difficult, but plaque shift is less pronounced. For LM bifurcation lesions requiring a two-stent technique with SB angulation 70 degrees or greater, a T-stent, modified T-stent, or TAP technique is usually performed.¹⁹⁵ If the SB angulation is less than 70 degrees, the crush, DK crush, or culotte technique is usually preferred.
4. Calcification severity and extent: Calcification extent and severity are underestimated by angiography compared with IVUS. If at least moderate calcification is present, plaque modification with either a cutting or scoring balloon or atherectomy is recommended. Although the necessity to perform atherectomy does not mandate a two-stent technique, such patients often have diffuse atherosclerotic disease, increasing the likelihood to benefit from an upfront two-stent approach.

DESCRIPTION OF TECHNIQUES

Culotte Technique

This technique (Figure 8.7 and Video 8.2) uses two stents and results in full coverage of the bifurcation area (especially the carina and SB ostium) but with two layers of metal in the proximal MV. The steps described here were used in the Nordic Stent Technique Study.¹³²

1. Wiring of both the MV and SB
2. Predilation of the MV, SB, or both (optional but recommended)
3. Stenting of the MV
4. Rewiring the SB through the MV stent and removal of the jailed wire in the SB
5. Dilation of the SB through the MV stent
6. Stenting the proximal MV and SB through the MV stent
7. Rewiring the MV through the SB stent
8. Final kissing balloon inflation

Typically, the first stent should be placed in the branch with the most angulated entry, whether it is the MB or SB. To allow full opening of the SB and preservation of the SB stent architecture, an open cell design stent, rather than a closed cell design, should be used when performing culotte stenting. Also, this technique should not be used if a large difference (≥ 1.5 mm) in vessel diameter between the MV and SB exists.¹⁹⁶

Crush Techniques

This technique (Figure 8.8 and Video 8.3) was first described by Colombo et al.,^{123,197,198} and it has undergone a few iterations over time.

1. Wiring of both the MV and SB
2. Predilation of the MV, SB, or both (optional but recommended)
3. Stenting of the SB first with an uninflated stent (or balloon) positioned in the MV. The proximal end of the SB stent should be several millimeters in the MV, but the proximal edge of the uninflated MV stent (or balloon) must be proximal to the proximal edge of the SB stent.
4. Assessing patency and flow in the SB to ensure an additional SB stent or immediate balloon angioplasty is not required
5. Removing the SB wire and stent balloon
6. Crushing the SB stent with the MV stent or balloon inflation (followed by the MV stent)
7. Rewiring the SB through the MV stent
8. High-pressure inflation of SB (optional)
9. Final kissing balloon inflation (mandatory)

Some variants of this technique have been described. Today, most operators try to minimize the length (2–3 mm) of the SB stent within the MV to reduce the multiple layers of crumpled stent (minicrush technique).^{195,199} If the SB stent is crushed within the MV stent, it is called the internal or reverse crush technique. In another variant, the MV stent is crushed by the SB stent (inverted crush technique).²⁰⁰ Another variant was developed to make this technique feasible by radial approach using a 6-Fr catheter. In this technique, the balloon is used to crush the SB stent, and the two stents are advanced and deployed sequentially

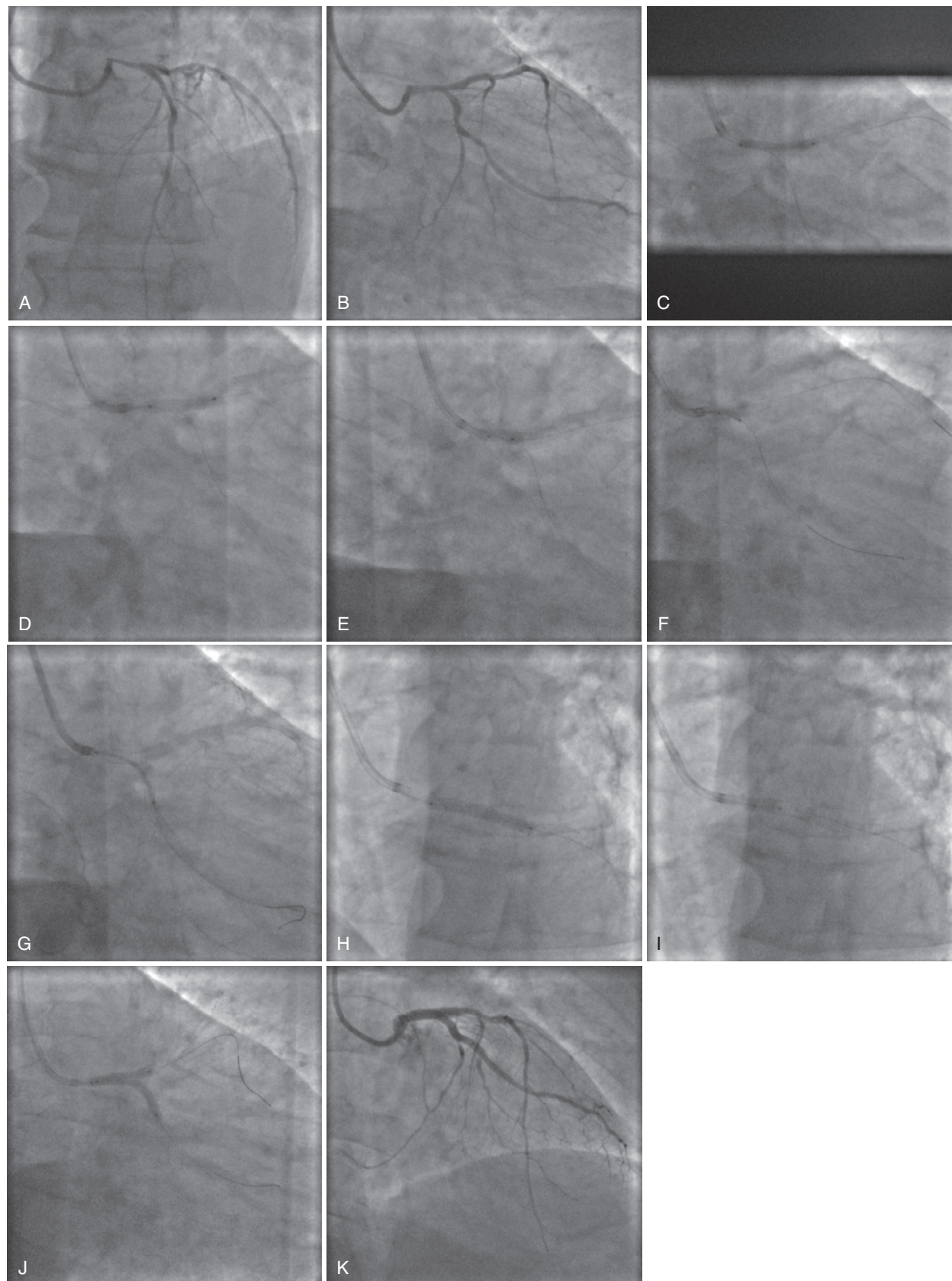


FIGURE 8.7 Left main coronary artery (LM) percutaneous coronary intervention using a two-stent culotte technique with final kissing (see also [Video 8.2](#)). **A**, Baseline angiogram showing severe LM disease with involvement of the proximal left anterior descending coronary artery (LAD). **B**, An intermediate lesion of the ostial left circumflex (LCX) and more severe lesion of the proximal LCX. **C**, Predilation of the LM and LAD. **D**, Stent implantation in the LM–LAD axis. **E**, Balloon inflation of the LM segment of the previously deployed stent, just proximal to the LCX ostium, using a short noncompliant balloon (proximal optimization technique [POT]). **F**, After removal of the LCX wire and rewiring of the LCX, predilation of the ostial LCX through the LM stent. **G**, After removal of the wire in the LAD, placement of the LM–LCX stent, through the first deployed LM–LAD stent. **H**, Stent implantation in the LM–LCX axis. **I**, Balloon inflation of the LM segment of the previously deployed stent, just proximal to the LAD ostium, using a short noncompliant balloon (POT). **J**, After rewiring of the LAD, simultaneous final kissing. **K**, Final angiogram showing an excellent result.

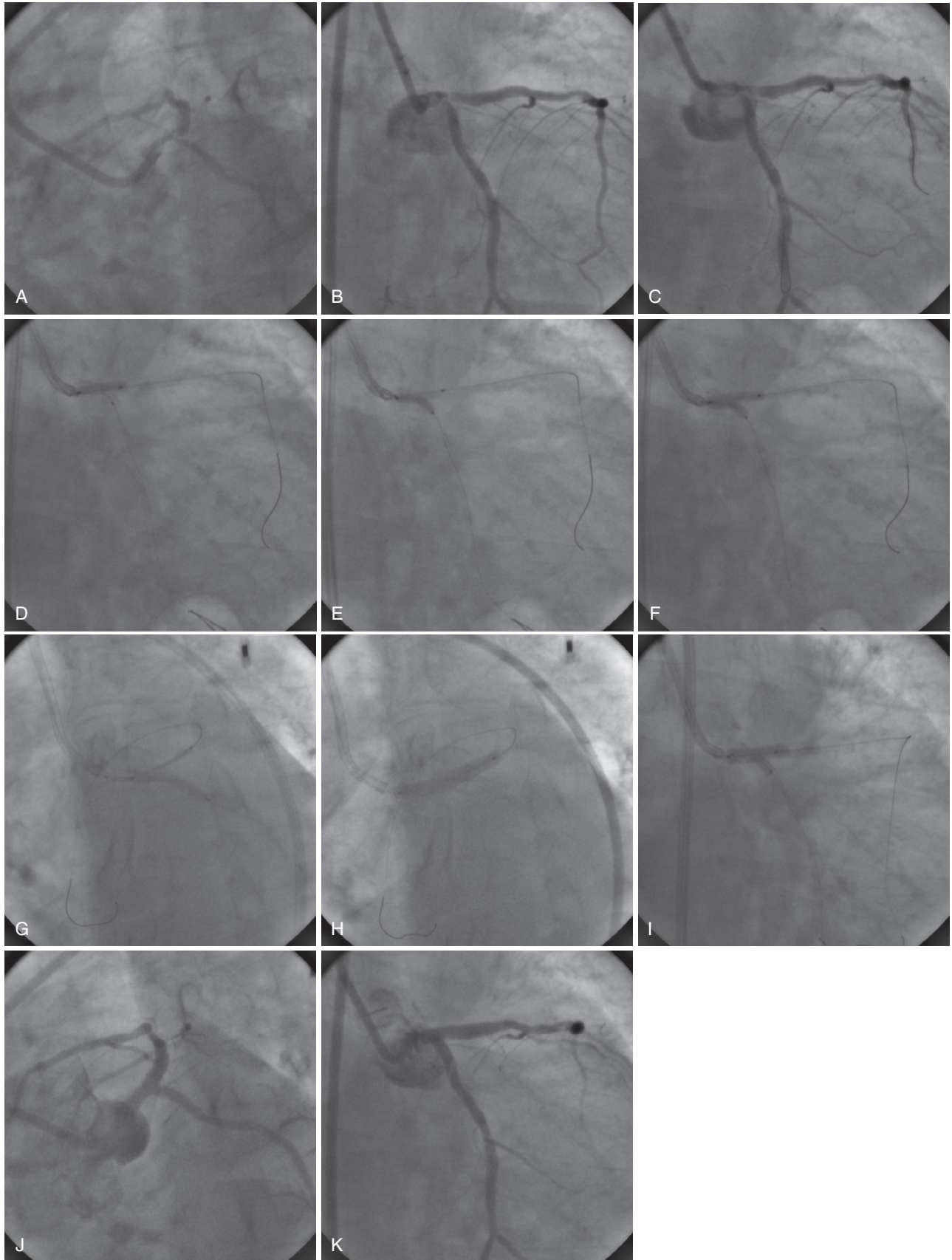


FIGURE 8.8 Left main coronary artery (LM) percutaneous coronary intervention using a two-stent crush technique with final kissing (see also [Video 8.3](#)). **A** and **B**, Baseline angiogram showing severe lesions involving the distal LM, the ostial left anterior descending coronary artery (LAD), and the ostial left circumflex (LCX; Medina 1-1-1 bifurcation). **C**, Wiring of the two branches. **D**, Predilatation of the LAD. **E**, Predilatation of the LCX. **F**, Simultaneous kissing predilatation. **G**, Two stents are simultaneously positioned in the bifurcation lesion: the eventually crushed stent (LCX) is positioned in the LCX, with minimal (~2–3 mm) protrusion in the LM. The “crushing” stent is positioned in the LM–LAD axis. The LCX stent is deployed first, with the LM–LAD stent in place but not deployed. **H**, After removal of the LCX stent balloon and wire, deployment of the LM–LAD stent, crushing the LM and carina portion of the previously deployed LCX stent. **I**, After rewiring of the LCX through the crushed stent, final kissing inflation. **J** and **K**, An excellent final result.

(step crush or modified balloon crush technique). Disadvantages of the crush technique include difficulty in SB rewiring for final kissing inflation and the presence of multiple layers of crumpled stent at the SB ostium, substantially increasing the rate of SB ostial ISR. In cases of difficult rewiring with conventional wire, a hydrophilic wire may be helpful in crossing into the SB. The most recent iteration of this technique is the DK crush,^{125,133,201} which involves two instances of balloon kissing, the first after the SB stent is crushed (facilitating rewiring for final kissing) and the second (final kiss) after deployment of the MV stent (Figure 8.9 and Video 8.4).

T-Stent Techniques

T-stent techniques (Figure 8.10 and Video 8.5) are used when SB stenting is required after a suboptimal result with provisional stenting or in a planned two-stent approach when the angle into the SB is 70 degrees or more but 100 degrees or less.

1. Wiring of the MV and SB
2. Dilation of the MV, SB, or both (recommended but optional).
3. Stenting the MV with the wire in place in the SB (alternatively, SB may be stented first)
4. Rewiring the SB and removing the jailed wire
5. Dilation of the SB through the MV stent
6. Stenting the SB through the MV stent with no stent protrusion in the MV (or placement of the MV stent if the SB was stented first)
7. Final kissing balloon inflation

The main disadvantage of this technique is the high rate of ostial restenosis of the SB because of suboptimal stent coverage in the bifurcation area, particularly the ostium; however, full coverage is possible with this technique if the angle into the SB from the MV is near 90 degrees. Alternatively, the TAP technique, with intentional minimal protrusion of the SB stent within the MV, may be performed when dealing with bifurcation angle larger than 70 degrees. After stenting of the MV, the SB stent is positioned in the SB with minimal protrusion in the MV, with a deflated balloon concurrently positioned in the MV. After inflation of the SB stent, the stent balloon is removed from the SB, and the MV balloon is inflated. After rewiring of the SB, a final kissing inflation is performed. If performed correctly, this technique increases the likelihood of complete coverage of the ostium without deformation of the stent or malapposed struts.

V-Stent Techniques

- ▶ In this technique (Figure 8.11 and Video 8.6), both the MV and SB are stented simultaneously. It is mainly used for distal disease in bifurcation (Medina 0, 1, 1).

1. Wiring of the MV and SB
2. Predilation of the MV and SB
3. Placement of stents in both branches with minimal proximal protrusion in MV

4. Placement of balloons in both branches and simultaneous (or sequential) deployment of stents
5. Final kissing balloon inflation

In cases with proximal disease (Medina 1, 1, 1), both stents are lined up in the LM shaft, creating a new carina; this approach is called the Y technique, simultaneous kissing stents, or double-barrel technique. In another variant of this technique for cases of extensive proximal disease in the MV, a proximal stent is first implanted before the bifurcation stenting; this is termed the skirt or extended Y technique. Y stenting is rarely used because the new carina is often eccentric and difficult to rewire in cases of ISR, and if a proximal dissection develops, it must be converted into a crush or culotte, a complex procedure. MACE rates have also been reported to be high after Y stenting.^{202,203} Y stenting may be useful, however, in a patient with hemodynamic instability in whom rapid stabilization of a high-grade LM stenosis is the main priority.

OSTIAL LEFT MAIN CORONARY ARTERY PERCUTANEOUS CORONARY INTERVENTION

When the LM length allows for a single stent implantation, PCI of the LM ostium is usually straightforward. Challenges related to this ostial LM stenting include proper assessment of the stenosis (spasm, angulation, severity), the potential for guide catheter-induced stent damage (longitudinal compression), systemic stent embolization if a short stent is deployed (an 8-mm stent should rarely be deployed in the ostial LM), retrograde sinus or aortic dissection, and difficulty to subsequently reengage the LM ostium in case of excessive stent protrusion into the aorta (Figure 8.12). Dedicated devices exist to help and guide more precise stent deployment in case of ostial lesions (e.g., Ostial Pro, Merit Medical Systems).

CONCLUSIONS

Revascularization decisions for patients with LM CAD are complex, requiring appropriate lesion assessment from noninvasive and invasive testing and risk stratification with prognostic instruments such the anatomic SYNTAX score and the clinical and anatomic SYNTAX score II, paired with a formal multidisciplinary heart team discussion. Patients with LM with extensive multivessel CAD are best managed by CABG; however, current evidence from RCTs suggests that PCI may provide at least equivalent results to CABG in selected LM patients with simple or moderately complex coronary anatomy. Given the large amount of myocardium supplied, LM PCI is inherently a high-risk procedure, and the results depend on operator expertise and experience, factors that must be taken into account in heart team discussions.

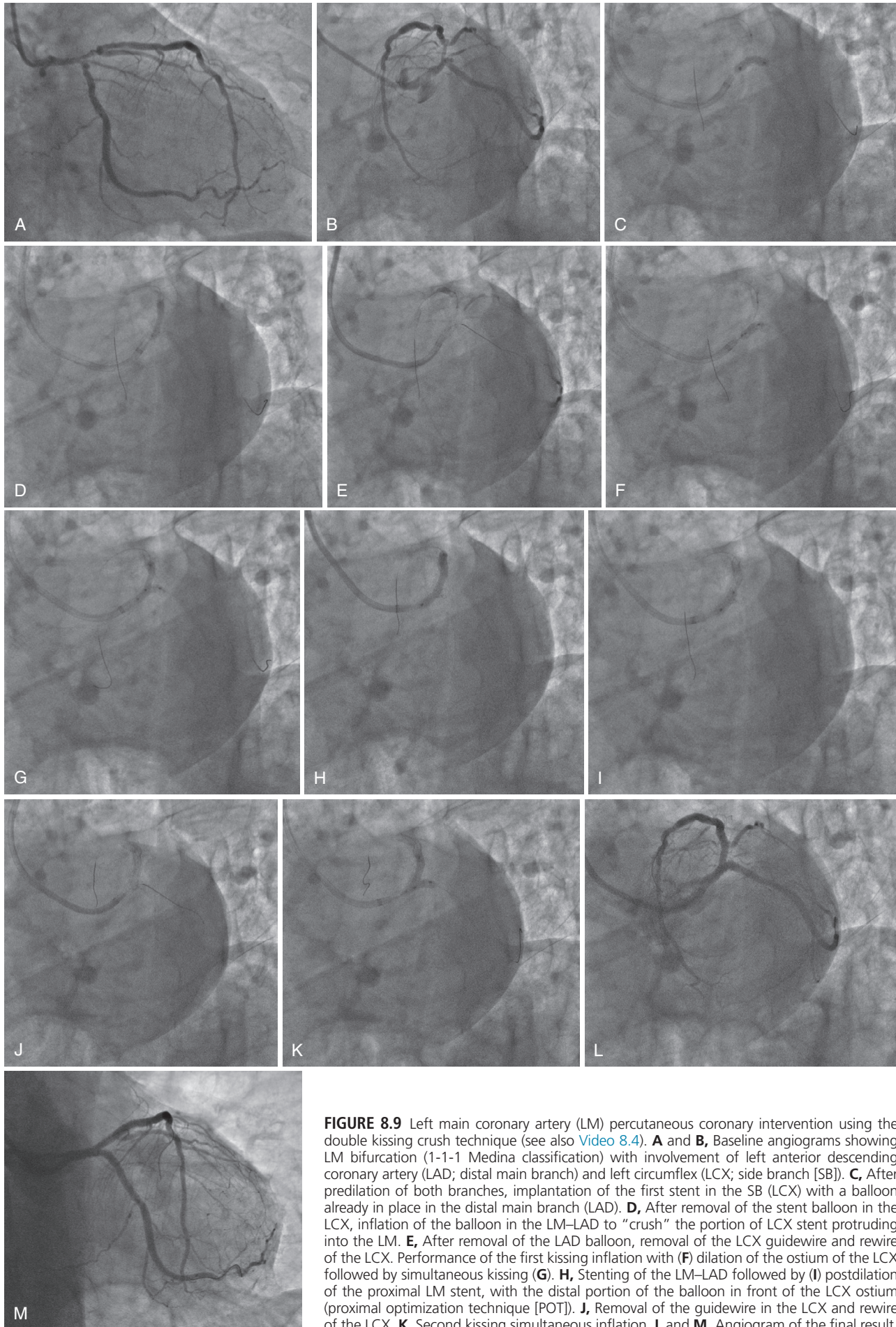


FIGURE 8.9 Left main coronary artery (LM) percutaneous coronary intervention using the double kissing crush technique (see also [Video 8.4](#)). **A** and **B**, Baseline angiograms showing LM bifurcation (1-1-1 Medina classification) with involvement of left anterior descending coronary artery (LAD; distal main branch) and left circumflex (LCX; side branch [SB]). **C**, After predilation of both branches, implantation of the first stent in the SB (LCX) with a balloon already in place in the distal main branch (LAD). **D**, After removal of the stent balloon in the LCX, inflation of the balloon in the LM-LAD to “crush” the portion of LCX stent protruding into the LM. **E**, After removal of the LAD balloon, removal of the LCX guidewire and rewiring of the LCX. Performance of the first kissing inflation with **(F)** dilation of the ostium of the LCX followed by simultaneous kissing **(G)**. **H**, Stenting of the LM-LAD followed by **(I)** postdilation of the proximal LM stent, with the distal portion of the balloon in front of the LCX ostium (proximal optimization technique [POT]). **J**, Removal of the guidewire in the LCX and rewiring of the LCX. **K**, Second kissing simultaneous inflation. **L** and **M**, Angiogram of the final result.

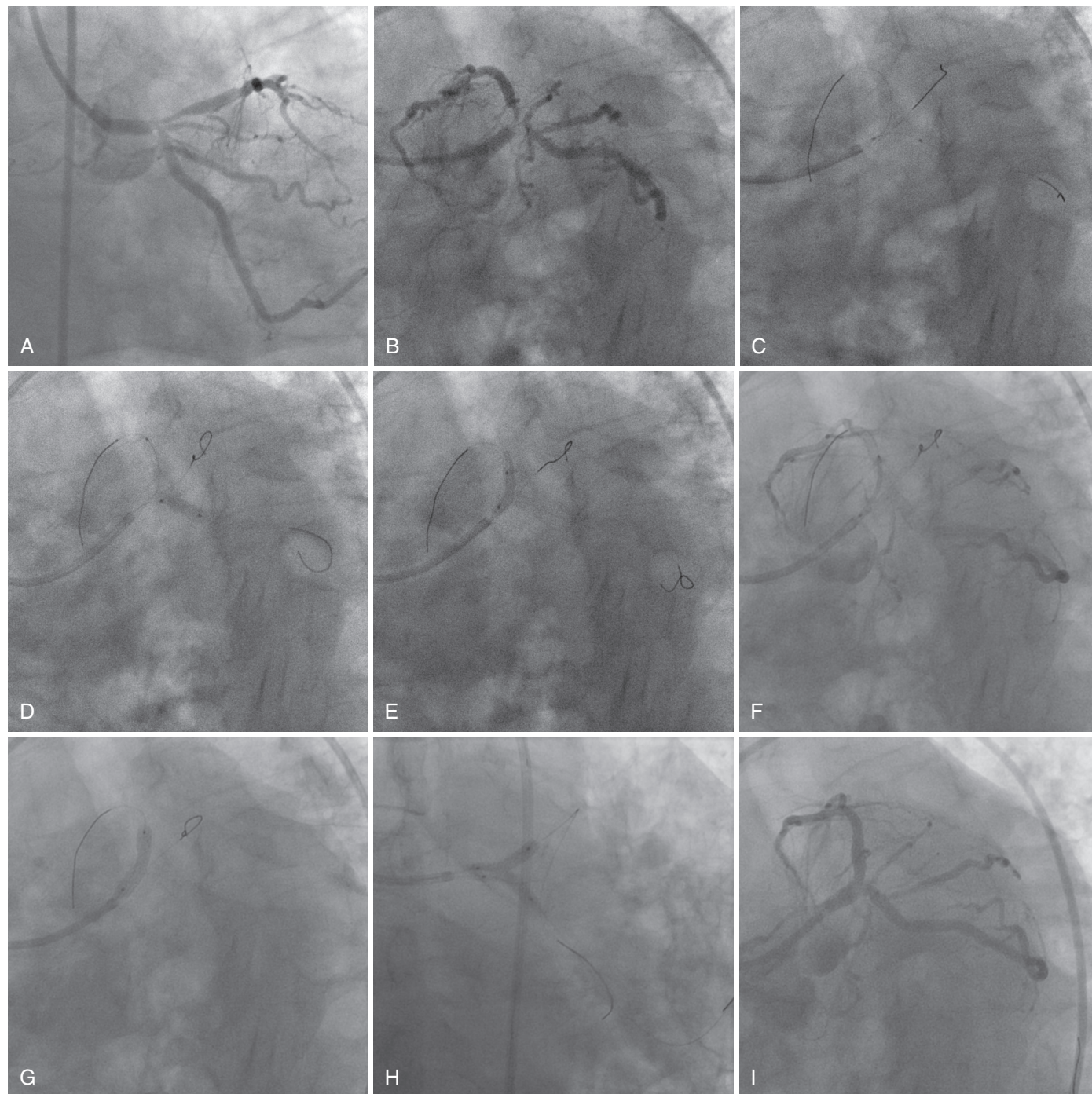


FIGURE 8.10 Left main coronary artery (LM) percutaneous coronary intervention using a two-stent T-stent technique (see also [Video 8.5](#)). **A** and **B**, Baseline angiogram showing a trifurcation lesion involving the distal LM, left anterior descending coronary artery (LAD), left circumflex (LCX), and ramus. A sharp angle (~90 degrees) is present between the LM and the LCX, making this favorable for a T-stent technique. **C**, Predilation of the LCX. **D**, Stent implantation in the LCX, with minimal protrusion of the LCX stent in the LM. Note the wire in the LAD and ramus helping to position the stent in the LCX. **E**, Predilation of the LAD after LCX stent deployment. If LCX struts were protruding in the LM, they would have been crushed, facilitating stent passage into the LAD. **F**, Stent placement in the LM–LAD axis. **G**, Stent deployment in the LM–LAD axis. **H**, After removal and rewiring of the LCX, final kissing inflation. **I**, Final angiogram showing an excellent result.

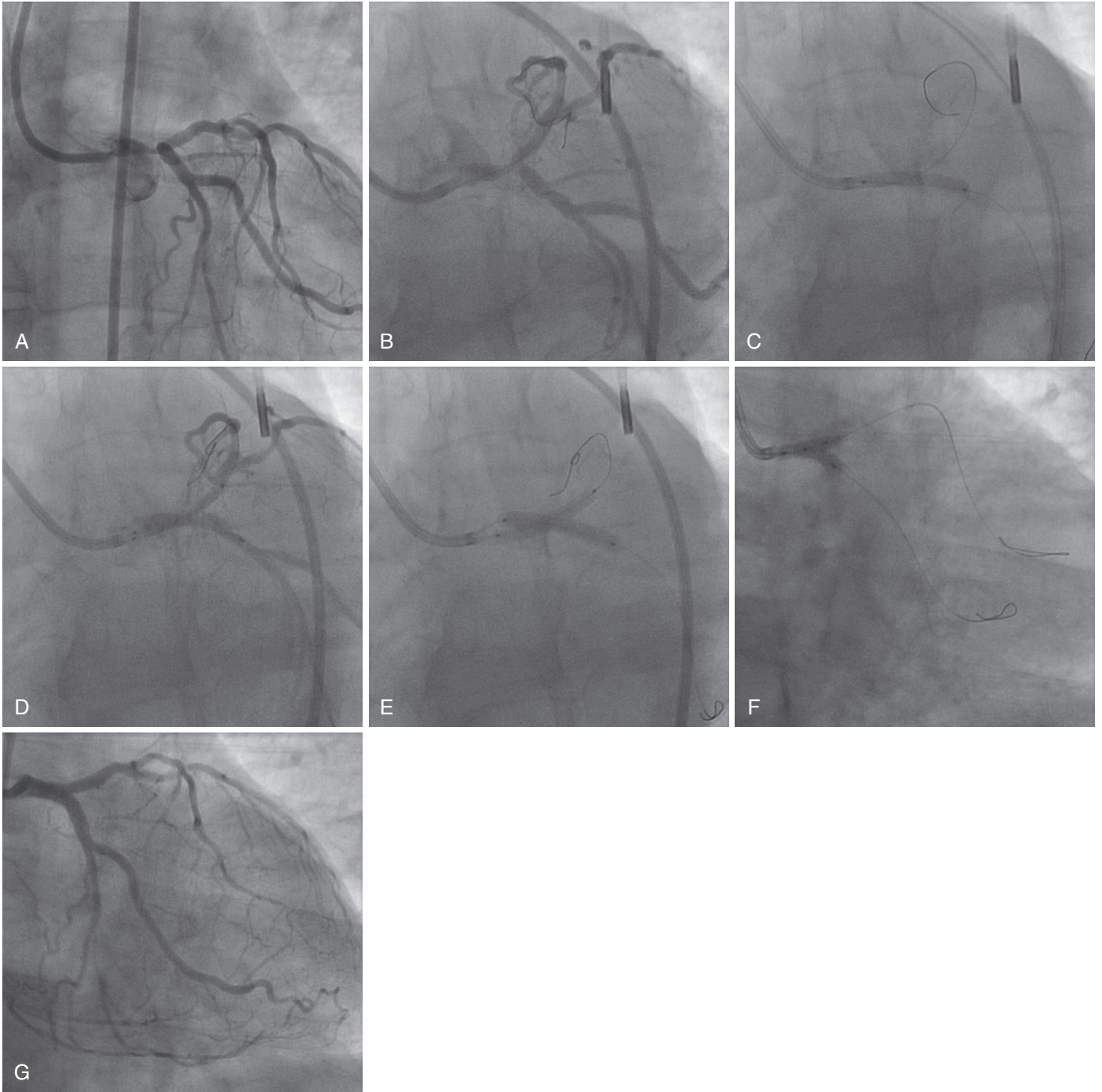


FIGURE 8.11 Left main coronary artery (LM) percutaneous coronary intervention using a two-stent V stenting (double-barrel) technique (see also [Video 8.6](#)). **A** and **B**, Baseline angiogram showing a bifurcation lesion involving the distal LM, the ostial left anterior descending coronary artery (LAD), and the ostial left circumflex (LCX; Medina bifurcation 1-1-1). **C**, Balloon predilation of the LCX. **D**, Simultaneous stent placement. **E**, Simultaneous stent deployment. **F**, Simultaneous postdilation (without removing the wires). **G**, Final angiogram showing an excellent result.

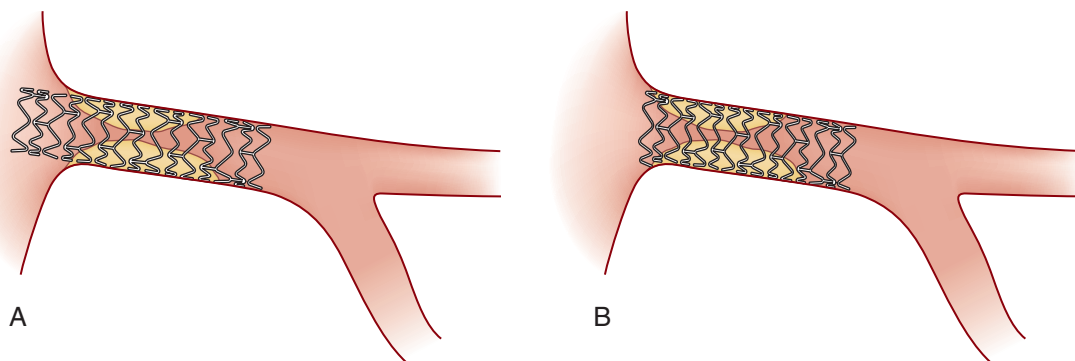


FIGURE 8.12 Percutaneous coronary intervention of an ostial left main coronary artery (LM) lesion. **A**, Stenting of LM with significant stent protrusion into the aorta. **B**, More desirable stenting of LM ostium with minimal stent protrusion into the aorta. (Modified from Park SJ. Presented at Left Main CTO Summit, New York; 2013.)

REFERENCES

- DeMots H, Rosch J, McNulty JH, Rahimtoola SH. Left main coronary artery disease. *Cardiovasc Clin*. 1977;8:201-211.
- Ragosta M, Dee S, Sarembock IJ, Lipson LC, Gimple LW, Powers ER. Prevalence of unfavorable angiographic characteristics for percutaneous intervention in patients with unprotected left main coronary artery disease. *Catheter Cardiovasc Interv*. 2006;68:357-362.
- Cohen MV, Cohn PF, Herman MV, Gorlin R. Diagnosis and prognosis of main left coronary artery obstruction. *Circulation*. 1972;45:157-165.
- Brennan JM, Dai D, Patel MR, et al. Characteristics and long-term outcomes of percutaneous revascularization of unprotected left main coronary artery stenosis in the United States: a report from the National Cardiovascular Data Registry, 2004 to 2008. *J Am Coll Cardiol*. 2012;59:648-654.
- Collet C, Capodanno D, Onuma Y, et al. Left main coronary artery disease: pathophysiology, diagnosis, and treatment. *Nat Rev Cardiol*. 2018;15:321-331.
- Taylor HA, Deumite NJ, Chaitman BR, Davis KB, Killip T, Rogers WJ. Asymptomatic left main coronary artery disease in the Coronary Artery Surgery Study (CASS) registry. *Circulation*. 1989;79:1171-1179.
- Chaitman BR, Fisher LD, Bourassa MG, et al. Effect of coronary bypass surgery on survival patterns in subsets of patients with left main coronary artery disease. Report of the Collaborative Study in Coronary Artery Surgery (CASS). *Am J Cardiol*. 1981;48:765-777.
- Cohen MV, Gorlin R. Main left coronary artery disease. Clinical experience from 1964-1974. *Circulation*. 1975;52:275-285.
- Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet*. 1994;344:563-570.
- Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASS experience. *Circulation*. 1995;91:2335-2344.
- Takaro T, Peduzzi P, Detre KM, et al. Survival in subgroups of patients with left main coronary artery disease. Veterans administration cooperative study of surgery for Coronary Arterial Occlusive Disease. *Circulation*. 1982;66:14-22.
- Campeau L, Corbara F, Crochet D, Petitclerc R. Left main coronary artery stenosis: the influence of aortocoronary bypass surgery on survival. *Circulation*. 1978;57:1111-1115.
- Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris. European Coronary Surgery Study Group. *Lancet*. 1982;2:1173-1180.
- Writing Committee M, Lawton JS, Tamis-Holland JE, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:197-215.
- Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
- Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol*. 2008;51:538-545.
- Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-972.
- Park SJ, Kim YH, Park DW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med*. 2011;364:1718-1727.
- Boudriot E, Thiele H, Walther T, et al. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. *J Am Coll Cardiol*. 2011;57:538-545.
- Stone GW, Sabik JF, Serruys PW, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med*. 2016;375:2223-2235.
- Makikallio T, Holm NR, Lindsay M, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet*. 2016;388:2743-2752.
- Holm NR, Makikallio T, Lindsay MM, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. *Lancet*. 2020;395:191-199.
- Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. 2013;381:629-638.
- Morice MC, Serruys PW, Kappetein AP, et al. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation*. 2014;129:2388-2394.
- Ahn JM, Roh JH, Kim YH, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease: 5-year outcomes of the PRECOMBAT Study. *J Am Coll Cardiol*. 2015;65:2198-2206.
- Park DW, Ahn JM, Park H, et al. Ten-year outcomes after drug-eluting stents versus coronary artery bypass grafting for left main coronary disease: extended follow-up of the PRECOMBAT trial. *Circulation*. 2020;141:1437-1446.
- Thuijs D, Kappetein AP, Serruys PW, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet*. 2019;394:1325-1334.
- Stone GW, Kappetein AP, Sabik JF, et al. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med*. 2019;381:1820-1830.
- Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation*. 2010;121:2645-2653.
- Shlofmitz E, Genereux P, Chen S, et al. Left main coronary artery disease revascularization according to the SYNTAX score. *Circ Cardiovasc Interv*. 2019;12:e008007.
- Athappan G, Patvardhan E, Tuzcu ME, Ellis S, Whitlow P, Kapadia SR. Left main coronary artery stenosis: a meta-analysis of drug-eluting stents versus coronary artery bypass grafting. *JACC Cardiovasc Interv*. 2013;6:1219-1230.
- Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. *J Am Coll Cardiol*. 2011;58:1426-1432.
- Palmerini T, Serruys P, Kappetein AP, et al. Clinical outcomes with percutaneous coronary revascularization vs coronary artery bypass grafting surgery in patients with unprotected left main coronary artery disease: a meta-analysis of 6 randomized trials and 4,686 patients. *Am Heart J*. 2017;190:54-63.
- Ahmad Y, Howard JP, Arnold AD, et al. Mortality after drug-eluting stents vs. coronary artery bypass grafting for left main coronary artery disease: a meta-analysis of randomized controlled trials. *Eur Heart J*. 2020;41:3228-3235.
- Gallo M, Blitzer D, Laforgia PL, et al. Percutaneous coronary intervention versus coronary artery bypass graft for left main coronary artery disease: a meta-analysis. *J Thorac Cardiovasc Surg*. 2022;163:94-105.e15.
- Kuno T, Ueyama H, Rao SV, et al. Percutaneous coronary intervention or coronary artery bypass graft surgery for left main coronary artery disease: a meta-analysis of randomized trials. *Am Heart J*. 2020;227:9-10.
- Sabatine MS, Bergmark BA, Murphy SA, et al. Percutaneous coronary intervention with drug-eluting stents versus coronary artery bypass grafting in left main coronary artery disease: an individual patient data meta-analysis. *Lancet*. 2021;398:2247-2257.

38. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;69:2212-2241.
39. Davidson LJ, Cleveland JC, Welt FG, et al. A practical approach to left main coronary artery disease: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;80:2119-2134.
40. Lamore K, Montalescot L, Untas A. Treatment decision-making in chronic diseases: what are the family members' roles, needs and attitudes? A systematic review. *Patient Educ Couns*. 2017;100:2172-2181.
41. Stacey D, Bennett CL, Barry MJ, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2011;CD001431.
42. Lin GA, Fagerlin A. Shared decision making: state of the science. *Circ Cardiovasc Qual Outcomes*. 2014;7:328-334.
43. Ting HH, Brito JP, Montori VM. Shared decision making: science and action. *Circ Cardiovasc Qual Outcomes*. 2014;7:323-327.
44. Hughes TM, Merath K, Chen Q, et al. Association of shared decision-making on patient-reported health outcomes and healthcare utilization. *Am J Surg*. 2018;216:7-12.
45. Bonzel T, Schachinger V, Dorge H. Description of a Heart Team approach to coronary revascularization and its beneficial long-term effect on clinical events after PCI. *Clin Res Cardiol*. 2016;105:388-400.
46. Chu D, Anastasio MM, Mulukutla SR, et al. Safety and efficacy of implementing a multidisciplinary heart team approach for revascularization in patients with complex coronary artery disease: an observational cohort pilot study. *JAMA Surg*. 2014;149:1109-1112.
47. Leonardi S, Marino M, Crimi G, et al. Appropriateness of percutaneous coronary interventions in patients with ischaemic HEart disease in Italy: the APACHE pilot study. *BMJ Open*. 2017;7:e016909.
48. Pavlidis AN, Perera D, Karamasis GV, et al. Implementation and consistency of Heart Team decision-making in complex coronary revascularisation. *Int J Cardiol*. 2016;206:37-41.
49. Sanchez CE, Dota A, Badhwar V, et al. Revascularization heart team recommendations as an adjunct to appropriate use criteria for coronary revascularization in patients with complex coronary artery disease. *Catheter Cardiovasc Interv*. 2016;88:E103-E112.
50. Yamasaki M, Abe K, Horikoshi R, et al. Enhanced outcomes for coronary artery disease obtained by a multidisciplinary heart team approach. *Gen Thorac Cardiovasc Surg*. 2019;67:841-848.
51. Patterson T, McConkey HZR, Ahmed-Jushuf F, et al. Long-term outcomes following heart team revascularization recommendations in complex coronary artery disease. *J Am Heart Assoc*. 2019;8:e011279.
52. Bittl JA, He Y, Jacobs AK, Yancy CW, Normand SL, American College of Cardiology Foundation/American Heart Association Task Force on Practice G. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. *Circulation*. 2013;127:2177-2185.
53. Talano JV, Scanlon PJ, Meadows WR, Kahn M, Pifarre R, Gunnar RM. Influence of surgery on survival in 145 patients with left main coronary artery disease. *Circulation*. 1975;52(2 suppl):1105-1111.
54. de la Torre Hernandez JM, Hernandez Hernandez F, Alfonso F, et al. Prospective application of pre-defined intravascular ultrasound criteria for assessment of intermediate left main coronary artery lesions results from the multicenter LITRO study. *J Am Coll Cardiol*. 2011;58:351-358.
55. Jasti V, Ivan E, Yalamanchili V, Wongpraparut N, Leeser MA. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation*. 2004;110:2831-2836.
56. Kang SJ, Lee JY, Ahn JM, et al. Intravascular ultrasound-derived predictors for fractional flow reserve in intermediate left main disease. *JACC Cardiovasc Interv*. 2011;4:1168-1174.
57. Park SJ, Ahn JM, Kang SJ, et al. Intravascular ultrasound-derived minimal lumen area criteria for functionally significant left main coronary artery stenosis. *JACC Cardiovasc Interv*. 2014;7:868-874.
58. Fassa AA, Wagatsuma K, Higano ST, et al. Intravascular ultrasound-guided treatment for angiographically indeterminate left main coronary artery disease: a long-term follow-up study. *J Am Coll Cardiol*. 2005;45:204-211.
59. Andell P, Karlsson S, Mohammad MA, et al. Intravascular ultrasound guidance is associated with better outcome in patients undergoing unprotected left main coronary artery stenting compared with angiography guidance alone. *Circ Cardiovasc Interv*. 2017;10:e004813.
60. Ladwiniec A, Walsh SJ, Holm NR, et al. Intravascular ultrasound to guide left main stem intervention: a NOBLE trial substudy. *EuroIntervention*. 2020;16:201-209.
61. Bavishi C, Sardar P, Chatterjee S, et al. Intravascular ultrasound-guided vs angiography-guided drug-eluting stent implantation in complex coronary lesions: meta-analysis of randomized trials. *Am Heart J*. 2017;185:26-34.
62. Buccheri S, Franchina G, Romano S, et al. Clinical outcomes following intravascular imaging-guided versus coronary angiography-guided percutaneous coronary intervention with stent implantation: a systematic review and Bayesian network meta-analysis of 31 studies and 17,882 patients. *JACC Cardiovasc Interv*. 2017;10:2488-2498.
63. Elgendy IY, Mahmoud AN, Elgendy AY, Bavry AA. Outcomes with intravascular ultrasound-guided stent implantation: a meta-analysis of randomized trials in the era of drug-eluting stents. *Circ Cardiovasc Interv*. 2016;9:e003700.
64. Hong SJ, Kim BK, Shin DH, et al. Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JAMA*. 2015;314:2155-2163.
65. Zhang J, Gao X, Kan J, et al. Intravascular ultrasound versus angiography-guided drug-eluting stent implantation: the ULTIMATE trial. *J Am Coll Cardiol*. 2018;72:3126-3137.
66. Kim BK, Shin DH, Hong MK, et al. Clinical impact of intravascular ultrasound-guided chronic total occlusion intervention with zotarolimus-eluting versus biolimus-eluting stent implantation: randomized study. *Circ Cardiovasc Interv*. 2015;8:e002592.
67. Witzensbichler B, Maehara A, Weisz G, et al. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study. *Circulation*. 2014;129:463-470.
68. Gao XF, Ge Z, Kong XQ, et al. 3-Year Outcomes of the ULTIMATE trial comparing intravascular ultrasound versus angiography-guided drug-eluting stent implantation. *JACC Cardiovasc Interv*. 2021;14:247-257.
69. Ali ZA, Maehara A, Genereux P, et al. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (LUMIEN III: OPTIMIZE PCI): a randomised controlled trial. *Lancet*. 2016;388:2618-2628.
70. Meneveau N, Souteyrand G, Motreff P, et al. Optical coherence tomography to optimize results of percutaneous coronary intervention in patients with non-ST-elevation acute coronary syndrome: results of the multicenter, randomized DOCTORS Study (Does Optical Coherence Tomography Optimize Results of Stenting?). *Circulation*. 2016;134:906-917.
71. Antonsen L, Thayssen P, Maehara A, et al. Optical Coherence Tomography Guided Percutaneous Coronary Intervention With Nobori Stent Implantation in Patients With Non-ST-Segment-Elevation Myocardial Infarction (OCTACS) trial: difference in strut coverage and dynamic malapposition patterns at 6 months. *Circ Cardiovasc Interv*. 2015;8:e002446.
72. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1:219-227.
73. Genereux P, Palmerini T, Caixeta A, et al. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. *Circ Cardiovasc Interv*. 2011;4:553-561.
74. Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet*. 2018;391:939-948.
75. Milojevic M, Serruys PW, Sabik JF 3rd, et al. Bypass surgery or stenting for left main coronary artery disease in patients with diabetes. *J Am Coll Cardiol*. 2019;73:1616-1628.
76. O'Neill WW, Kleiman NS, Moses J, et al. A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: the PROTECT II study. *Circulation*. 2012;126:1717-1727.
77. Perera D, Stables R, Thomas M, et al. Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2010;304:867-874.
78. Osnabrugge RL, Speir AM, Head SJ, et al. Performance of EuroSCORE II in a large US database: implications for transcatheter aortic valve implantation. *Eur J Cardiothorac Surg*. 2014;46:400-408; discussion 408.
79. Kirmani BH, Mazhar K, Fabri BM, Pullan DM. Comparison of the EuroSCORE II and Society of Thoracic Surgeons 2008 risk tools. *Eur J Cardiothorac Surg*. 2013;44:999-1005; discussion.
80. Ad N, Holmes SD, Patel J, Pritchard G, Shuman DJ, Halpin L. Comparison of EuroSCORE II, Original EuroSCORE, and The Society of Thoracic Surgeons Risk Score in Cardiac Surgery Patients. *Ann Thorac Surg*. 2016;102:573-579.
81. Wykrzykowska JJ, Garg S, Girasis C, et al. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. *J Am Coll Cardiol*. 2010;56:272-277.
82. Garg S, Serruys PW, Silber S, et al. The prognostic utility of the SYNTAX score on 1-year outcomes after revascularization with zotarolimus- and everolimus-eluting stents: a substudy of the RESOLUTE All Comers Trial. *JACC Cardiovasc Interv*. 2011;4:432-441.
83. Zhao M, Stampf S, Valina C, et al. Role of euroSCORE II in predicting long-term outcome after percutaneous catheter intervention for coronary triple vessel disease or left main stenosis. *Int J Cardiol*. 2013;168:3273-3279.
84. Cavalcante R, Sotomi Y, Mancone M, et al. Impact of the SYNTAX scores I and II in patients with diabetes and multivessel coronary disease: a pooled analysis of patient level data from the SYNTAX, PRECOMBAT, and BEST trials. *Eur Heart J*. 2017;38:1969-1977.
85. Head SJ, Davierwala PM, Serruys PW, et al. Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. *Eur Heart J*. 2014;35:2821-2830.
86. Dzavik V, Ghali WA, Norris C, et al. Long-term survival in 11,661 patients with multivessel coronary artery disease in the era of stenting: a report from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. *Am Heart J*. 2001;142:119-126.

87. Lee PH, Ahn JM, Chang M, et al. Left main coronary artery disease: secular trends in patient characteristics, treatments, and outcomes. *J Am Coll Cardiol*. 2016;68:1233-1246.
88. Cavalcante R, Sotomi Y, Lee CW, et al. Outcomes after percutaneous coronary intervention or bypass surgery in patients with unprotected left main disease. *J Am Coll Cardiol*. 2016;68:999-1009.
89. Giacoppo D, Collieran R, Cassese S, et al. Percutaneous coronary intervention vs coronary artery bypass grafting in patients with left main coronary artery stenosis: a systematic review and meta-analysis. *JAMA Cardiol*. 2017;2:1079-1088.
90. Park SJ, Kim YH, Park DW, et al. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv*. 2009;2:167-177.
91. Chen SL, Zhang JJ, Han Y, et al. Double kissing crush versus provisional stenting for left main distal bifurcation lesions: DKCRUSH-V randomized trial. *J Am Coll Cardiol*. 2017;70:2605-2617.
92. Yadav M, Palmerini T, Caixeta A, et al. Prediction of coronary risk by SYNTAX and derived scores: synergy between percutaneous coronary intervention with taxus and cardiac surgery. *J Am Coll Cardiol*. 2013;62:1219-1230.
93. Capodanno D, Capranzano P, Di Salvo ME, et al. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *JACC Cardiovasc Interv*. 2009;2:731-738.
94. Kim YH, Park DW, Kim WJ, et al. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score for prediction of outcomes after unprotected left main coronary revascularization. *JACC Cardiovasc Interv*. 2010;3:612-623.
95. Onuma Y, Girasis C, Piazza N, et al. Long-term clinical results following stenting of the left main stem: insights from RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries. *JACC Cardiovasc Interv*. 2010;3:584-594.
96. Capodanno D, Caggigi A, Capranzano P, et al. Validating the EXCEL hypothesis: a propensity score matched 3-year comparison of percutaneous coronary intervention versus coronary artery bypass graft in left main patients with SYNTAX score ≤ 32 . *Catheter Cardiovasc Interv*. 2011;77:936-943.
97. Chakravarty T, Buch MH, Naik H, et al. Predictive accuracy of SYNTAX score for predicting long-term outcomes of unprotected left main coronary artery revascularization. *Am J Cardiol*. 2011;107:360-366.
98. Shiohara H, Morimoto T, Hayano M, et al. Comparison of long-term outcome after percutaneous coronary intervention versus coronary artery bypass grafting in patients with unprotected left main coronary artery disease (from the CREDO-Kyoto PCI/CABG Registry Cohort-2). *Am J Cardiol*. 2012;110:924-932.
99. Tiroch K, Mehili J, Byrne RA, et al. Impact of coronary anatomy and stenting technique on long-term outcome after drug-eluting stent implantation for unprotected left main coronary artery disease. *JACC Cardiovasc Interv*. 2014;7:29-36.
100. Capodanno D, Miano M, Cincotta G, et al. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. *Am Heart J*. 2010;159:103-109.
101. Serruys PW, Farooq V, Vranckx P, et al. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years. *JACC Cardiovasc Interv*. 2012;5:606-617.
102. Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013;381:639-650.
103. Xu B, Genereux P, Yang Y, et al. Validation and comparison of the long-term prognostic capability of the SYNTAX score-II among 1,528 consecutive patients who underwent left main percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2014;7:1128-1137.
104. Palmerini T, Marzocchi A, Tamburino C, et al. Two-year clinical outcome with drug-eluting stents versus bare-metal stents in a real-world registry of unprotected left main coronary artery stenosis from the Italian Society of Invasive Cardiology. *Am J Cardiol*. 2008;102:1463-1468.
105. Erglis A, Narbutė I, Kumsars I, et al. A randomized comparison of paclitaxel-eluting stents versus bare-metal stents for treatment of unprotected left main coronary artery stenosis. *J Am Coll Cardiol*. 2007;50:491-497.
106. Kim YH, Park DW, Lee SW, et al. Long-term safety and effectiveness of unprotected left main coronary stenting with drug-eluting stents compared with bare-metal stents. *Circulation*. 2009;120:400-407.
107. Mehili J, Kastrati A, Byrne RA, et al. Paclitaxel- versus sirolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol*. 2009;53:1760-1768.
108. Mehili J, Richardt G, Valgimigli M, et al. Zotarolimus- versus everolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol*. 2013;62:2075-2082.
109. Kim YH, Park DW, Ahn JM, et al. Everolimus-eluting stent implantation for unprotected left main coronary artery stenosis. The PRECOMBAT-2 (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) study. *JACC Cardiovasc Interv*. 2012;5:708-717.
110. Moynagh A, Salvatella N, Harb T, et al. Two-year outcomes of everolimus vs. paclitaxel-eluting stent for the treatment of unprotected left main lesions: a propensity score matching comparison of patients included in the French Left Main Taxus (FLM Taxus) and the Left Main Xience (LEMAX) registries. *EuroIntervention*. 2013;9:452-462.
111. Pandya SB, Kim YH, Meyers SN, et al. Drug-eluting versus bare-metal stents in unprotected left main coronary artery stenosis: a meta-analysis. *JACC Cardiovasc Interv*. 2010;3:602-611.
112. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet*. 2012;379:1393-1402.
113. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation*. 2012;125:2873-2879.
114. Ojeda S, Pan M, Martin P, et al. Immediate results and long-term clinical outcome of patients with unprotected distal left main stenosis: the CORPAL registry (Cordoba and Las Palmas). *JACC Cardiovasc Interv*. 2014;7:212-221.
115. Ielasi A, Takagi K, Latib A, et al. Long-term clinical outcomes following drug-eluting stent implantation for unprotected distal trifurcation left main disease: the Milan-New Tokyo (MITO) registry. *Catheter Cardiovasc Interv*. 2014;83:530-538.
116. Kang SJ, Ahn JM, Song H, et al. Comprehensive intravascular ultrasound assessment of stent area and its impact on restenosis and adverse cardiac events in 403 patients with unprotected left main disease. *Circ Cardiovasc Interv*. 2011;4:562-569.
117. Naganuma T, Chieffo A, Meliga E, et al. Long-term clinical outcomes after percutaneous coronary intervention for ostial/mid-shaft lesions versus distal bifurcation lesions in unprotected left main coronary artery: the DELTA Registry (drug-eluting stent for left main coronary artery disease): a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Interv*. 2013;6:1242-1249.
118. Palmerini T, Sangiorgi D, Marzocchi A, et al. Ostial and midshaft lesions vs. bifurcation lesions in 1111 patients with unprotected left main coronary artery stenosis treated with drug-eluting stents: results of the survey from the Italian Society of Invasive Cardiology. *Eur Heart J*. 2009;30:2087-2094.
119. Colombo A, Moses JW, Morice MC, et al. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation*. 2004;109:1244-1249.
120. Pan M, de Lezo JS, Medina A, et al. Rapamycin-eluting stents for the treatment of bifurcated coronary lesions: a randomized comparison of a simple versus complex strategy. *Am Heart J*. 2004;148:857-864.
121. Steigen TK, Maeng M, Wiseth R, et al. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation*. 2006;114:1955-1961.
122. Ferenc M, Gick M, Kienzle RP, et al. Randomized trial on routine vs. provisional T-stenting in the treatment of de novo coronary bifurcation lesions. *Eur Heart J*. 2008;29:2859-2867.
123. Colombo A, Bramucci E, Sacca S, et al. Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurcations: the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) study. *Circulation*. 2009;119:71-78.
124. Song YB, Hahn JY, Song PS, et al. Randomized comparison of conservative versus aggressive strategy for provisional side branch intervention in coronary bifurcation lesions: results from the SMART-STRATEGY (Smart Angioplasty Research Team-Optimal Strategy for Side Branch Intervention in Coronary Bifurcation Lesions) randomized trial. *JACC Cardiovasc Interv*. 2012;5:1133-1140.
125. Chen SL, Santoso T, Zhang JJ, et al. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions: results from the DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) trial. *J Am Coll Cardiol*. 2011;57:914-920.
126. Hildick-Smith D, de Belder AJ, Cooter N, et al. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation*. 2010;121:1235-1243.
127. Hildick-Smith D, Egred M, Banning A, et al. The European bifurcation club Left Main Coronary Stent study: a randomized comparison of stepwise provisional vs. systematic dual stenting strategies (EBC MAIN). *Eur Heart J*. 2021;42:3829-3839.
128. Kandzari DE, Gershlick AH, Serruys PW, et al. Outcomes among patients undergoing distal left main percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2018;11:e007007.
129. Albiero R, Burzotta F, Lassen JF, et al. Treatment of coronary bifurcation lesions, part I: implanting the first stent in the provisional pathway. The 16th expert consensus document of the European Bifurcation Club. *EuroIntervention*. 2022;18:e362-e376.
130. Lassen JF, Albiero R, Johnson TW, et al. Treatment of coronary bifurcation lesions, part II: implanting two stents. The 16th expert consensus document of the European Bifurcation Club. *EuroIntervention*. 2022;18:457-470.
131. Zhang JJ, Ye F, Xu K, et al. Multicentre, randomized comparison of two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions: the DEFINITION II trial. *Eur Heart J*. 2020;41:2523-2536.
132. Erglis A, Kumsars I, Niemela M, et al. Randomized comparison of coronary bifurcation stenting with the crush versus the culotte technique using

- sirolimus eluting stents: the Nordic stent technique study. *Circ Cardiovasc Interv.* 2009;2:27-34.
133. Chen SL, Xu B, Han YL, et al. Comparison of double kissing crush versus Culotte stenting for unprotected distal left main bifurcation lesions: results from a multicenter, randomized, prospective DKCRUSH-III study. *J Am Coll Cardiol.* 2013;61:1482-1488.
 134. Genereux P, Kumsars I, Lesiak M, et al. A randomized trial of a dedicated bifurcation stent versus provisional stenting in the treatment of coronary bifurcation lesions. *J Am Coll Cardiol.* 2015;65:533-543.
 135. Magro M, Girasis C, Bartorelli AL, et al. Acute procedural and six-month clinical outcome in patients treated with a dedicated bifurcation stent for left main stem disease: the TRYTON LM multicentre registry. *EuroIntervention.* 2013;8:1259-1269.
 136. Grundeken MJ, Asgedom S, Damman P, et al. Six-month and one-year clinical outcomes after placement of a dedicated coronary bifurcation stent: a patient-level pooled analysis of eight registry studies. *EuroIntervention.* 2013;9:195-203.
 137. Hasegawa T, Ako J, Koo BK, et al. Analysis of left main coronary artery bifurcation lesions treated with biolimus-eluting DEVAX AXCESS plus nitinol self-expanding stent: intravascular ultrasound results of the AXENT trial. *Catheter Cardiovasc Interv.* 2009;73:34-41.
 138. Costa RA, Abizaid A, Abizaid AS, et al. Procedural and early clinical outcomes of patients with de novo coronary bifurcation lesions treated with the novel Nile PAX dedicated bifurcation polymer-free paclitaxel coated stents: results from the prospective, multicentre, non-randomised BIPAX clinical trial. *EuroIntervention.* 2012;7:1301-1309.
 139. Ge L, Airolidi F, Iakovou I, et al. Clinical and angiographic outcome after implantation of drug-eluting stents in bifurcation lesions with the crush stent technique: importance of final kissing balloon post-dilation. *J Am Coll Cardiol.* 2005;46:613-620.
 140. Chen SL, Zhang JJ, Ye F, et al. Effect of coronary bifurcation angle on clinical outcomes in Chinese patients treated with crush stenting: a subgroup analysis from DKCRUSH-1 bifurcation study. *Chin Med J (Engl).* 2009;122:396-402.
 141. Derimay F, Rioufol G, Nishi T, et al. Optimal balloon positioning for the proximal optimization technique? An experimental bench study. *Int J Cardiol.* 2019;292:95-97.
 142. Niemela M, Kervinen K, Erglis A, et al. Randomized comparison of final kissing balloon dilatation versus no final kissing balloon dilatation in patients with coronary bifurcation lesions treated with main vessel stenting: the Nordic-Baltic Bifurcation Study III. *Circulation.* 2011;123:79-86.
 143. Hamilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation.* 2009;120:1505-1512.
 144. Abizaid AS, Mintz GS, Abizaid A, et al. One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. *J Am Coll Cardiol.* 1999;34:707-715.
 145. Park SJ, Ahn JM, Kang SJ. Unprotected left main percutaneous coronary intervention: integrated use of fractional flow reserve and intravascular ultrasound. *J Am Heart Assoc.* 2012;1:e004556.
 146. Kinnaird T, Johnson T, Anderson R, et al. Intravascular imaging and 12-month mortality after unprotected left main stem PCI: an analysis from the British Cardiovascular Intervention Society Database. *JACC Cardiovasc Interv.* 2020;13:346-357.
 147. Maehara A, Mintz G, Serruys P, et al. Impact of final minimal stent area by IVUS on 3-year outcome after PCI of left main coronary artery disease: the EXCEL trial. *J Am Coll Cardiol.* 2017;69:963.
 148. Kubo T, Akasaka T, Shite J, et al. OCT compared with IVUS in a coronary lesion assessment: the OPUS-CLASS study. *JACC Cardiovasc Imaging.* 2013;6:1095-1104.
 149. Di Mario C, Iakovou I, van der Giessen WJ, et al. Optical coherence tomography for guidance in bifurcation lesion treatment. *EuroIntervention.* 2010;6(suppl J):J99-J106.
 150. Okamura T, Onuma Y, Yamada J, et al. 3D optical coherence tomography: new insights into the process of optimal rewiring of side branches during bifurcational stenting. *EuroIntervention.* 2014;10:907-915.
 151. Fujino Y, Attizzani GF, Bezerra HG, et al. Serial assessment of vessel interactions after drug-eluting stent implantation in unprotected distal left main coronary artery disease using frequency-domain optical coherence tomography. *JACC Cardiovasc Interv.* 2013;6:1035-1045.
 152. Fujino Y, Bezerra HG, Attizzani GF, et al. Frequency-domain optical coherence tomography assessment of unprotected left main coronary artery disease-a comparison with intravascular ultrasound. *Catheter Cardiovasc Interv.* 2013;82:E173-E183.
 153. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med.* 2009;360:213-224.
 154. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med.* 2012;367:991-1001.
 155. Melikian N, De Bondt P, Tonino P, et al. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. *JACC Cardiovasc Interv.* 2010;3:307-314.
 156. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med.* 1996;334:1703-1708.
 157. Koo BK, Kang HJ, Youn TJ, et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve. *J Am Coll Cardiol.* 2005;46:633-637.
 158. Koo BK, Park KW, Kang HJ, et al. Physiological evaluation of the provisional side-branch intervention strategy for bifurcation lesions using fractional flow reserve. *Eur Heart J.* 2008;29:726-732.
 159. Bech GJ, Droste H, Pijls NH, et al. Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease. *Heart.* 2001;86:547-552.
 160. Jimenez-Navarro M, Hernandez-Garcia JM, Alonso-Brales JH, et al. Should we treat patients with moderately severe stenosis of the left main coronary artery and negative FFR results? *J Invasive Cardiol.* 2004;16:398-400.
 161. Legutko J, Dudek D, Rzeszutko L, Wozniak M, Dubiel JS. Fractional flow reserve assessment to determine the indications for myocardial revascularisation in patients with borderline stenosis of the left main coronary artery. *Kardiol Pol.* 2005;63:499-506; discussion 507-508.
 162. Suemaru S, Iwasaki K, Yamamoto K, et al. Coronary pressure measurement to determine treatment strategy for equivocal left main coronary artery lesions. *Heart Vessels.* 2005;20:271-277.
 163. Lindstaedt M, Yazar A, Gerding A, et al. Clinical outcome in patients with intermediate or equivocal left main coronary artery disease after deferral of surgical revascularization on the basis of fractional flow reserve measurements. *Am Heart J.* 2006;152:156.e1-e9.
 164. Puri R, Kapadia SR, Nicholls SJ, Harvey JE, Kataoka Y, Tuzcu EM. Optimizing outcomes during left main percutaneous coronary intervention with intravascular ultrasound and fractional flow reserve: the current state of evidence. *JACC Cardiovasc Interv.* 2012;5:697-707.
 165. Pijls NH, De Bruyne B, Bech GJ, et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. *Circulation.* 2000;102:2371-2377.
 166. Vis MM, Beijl MA, Grundeken MJ, et al. A systematic review and meta-analysis on primary percutaneous coronary intervention of an unprotected left main coronary artery culprit lesion in the setting of acute myocardial infarction. *JACC Cardiovasc Interv.* 2013;6:317-324.
 167. Pedrazzini GB, Radovanovic D, Vassalli G, et al. Primary percutaneous coronary intervention for unprotected left main disease in patients with acute ST-segment elevation myocardial infarction the AMIS (Acute Myocardial Infarction in Switzerland) plus registry experience. *JACC Cardiovasc Interv.* 2011;4:627-633.
 168. Patel N, De Maria GL, Kassimis G, et al. Outcomes after emergency percutaneous coronary intervention in patients with unprotected left main stem occlusion: the BCIS national audit of percutaneous coronary intervention 6-year experience. *JACC Cardiovasc Interv.* 2014;7:969-980.
 169. Briguori C, Airolidi F, Chieffo A, et al. Elective versus provisional intra-aortic balloon pumping in unprotected left main stenting. *Am Heart J.* 2006;152:565-572.
 170. Mishra S, Chu WW, Torguson R, et al. Role of prophylactic intra-aortic balloon pump in high-risk patients undergoing percutaneous coronary intervention. *Am J Cardiol.* 2006;98:608-612.
 171. Briguori C, Sarais C, Pagnotta P, et al. Elective versus provisional intra-aortic balloon pumping in high-risk percutaneous transluminal coronary angioplasty. *Am Heart J.* 2003;145:700-707.
 172. Dixon SR, Henriques JP, Mauri L, et al. A prospective feasibility trial investigating the use of the Impella 2.5 system in patients undergoing high-risk percutaneous coronary intervention (The PROTECT I Trial): initial U.S. experience. *JACC Cardiovasc Interv.* 2009;2:91-96.
 173. Genereux P, Giustino G, Redfors B, et al. Impact of percutaneous coronary intervention extent, complexity and platelet reactivity on outcomes after drug-eluting stent implantation. *Int J Cardiol.* 2018;268:61-67.
 174. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and safety of dual antiplatelet therapy after complex PCI. *J Am Coll Cardiol.* 2016;68:1851-1864.
 175. Stone GW, Genereux P, Harrington RA, et al. Impact of lesion complexity on peri-procedural adverse events and the benefit of potent intravenous platelet adenosine diphosphate receptor inhibition after percutaneous coronary intervention: core laboratory analysis from 10 854 patients from the CHAMPION PHOENIX trial. *Eur Heart J.* 2018;39:4112-4121.
 176. Jang WJ, Ahn SG, Song YB, et al. Benefit of prolonged dual antiplatelet therapy after implantation of drug-eluting stent for coronary bifurcation lesions: results from the Coronary Bifurcation Stenting Registry II. *Circ Cardiovasc Interv.* 2018;11:e005849.
 177. Yeh RW, Kereiakes DJ, Steg PG, et al. Lesion complexity and outcomes of extended dual antiplatelet therapy after percutaneous coronary intervention. *J Am Coll Cardiol.* 2017;70:2213-2223.
 178. Choi J, Kim IS, Cho S, et al. Optimal duration for dual antiplatelet therapy after left main coronary artery stenting. *Circ J.* 2020;85:59-68.
 179. D'Ascenzo F, Barbero U, Abdirashid M, et al. Incidence of adverse events at 3 months versus at 12 months after dual antiplatelet therapy cessation in patients treated with thin stents with unprotected left main or coronary bifurcations. *Am J Cardiol.* 2020;125:491-499.
 180. van Geuns RJ, Chun-Chin C, McEntegart MB, et al. Bioabsorbable polymer drug-eluting stents with 4-month dual antiplatelet therapy versus durable polymer drug-eluting stents with 12-month dual antiplatelet therapy in patients with left main coronary artery disease: the IDEAL-LM randomised trial. *EuroIntervention.* 2022;17:1467-1476.
 181. Cho S, Kim JS, Kang TS, et al. Long-term efficacy of extended dual antiplatelet therapy after left main coronary artery bifurcation stenting. *Am J Cardiol.* 2020;125:320-327.



182. Wang HY, Dou KF, Guan C, et al. New insights into long- versus short-term dual antiplatelet therapy duration in patients after stenting for left main coronary artery disease: findings from a prospective observational study. *Circ Cardiovasc Interv.* 2022;15:e011536.
183. Brener SJ, Serruys PW, Morice MC, et al. Optimal duration of dual antiplatelet therapy after left main coronary stenting. *J Am Coll Cardiol.* 2018;72:2086-2087.
184. Chiarito M, Kini A, Roumeliotis A, et al. Prevalence and impact of high bleeding risk in patients undergoing left main artery disease PCI. *JACC Cardiovasc Interv.* 2021;14:2447-2457.
185. Farooq V, Serruys PW, Zhang Y, et al. Short-term and long-term clinical impact of stent thrombosis and graft occlusion in the SYNTAX trial at 5 years: synergy between percutaneous coronary intervention with Taxus and cardiac Surgery trial. *J Am Coll Cardiol.* 2013;62:2360-2399.
186. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA.* 2005;293:2126-2130.
187. Palmerini T, Marzocchi A, Tamburino C, et al. Temporal pattern of ischemic events in relation to dual antiplatelet therapy in patients with unprotected left main coronary artery stenosis undergoing percutaneous coronary intervention. *J Am Coll Cardiol.* 2009;53:1176-1181.
188. Airolidi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation.* 2007;116:745-754.
189. Park DW, Yun SC, Lee SW, et al. Stent thrombosis, clinical events, and influence of prolonged clopidogrel use after placement of drug-eluting stent data from an observational cohort study of drug-eluting versus bare-metal stents. *JACC Cardiovasc Interv.* 2008;1:494-503.
190. Schulz S, Schuster T, Mehilli J, et al. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. *Eur Heart J.* 2009;30:2714-2721.
191. Migliorini A, Valenti R, Marcucci R, et al. High residual platelet reactivity after clopidogrel loading and long-term clinical outcome after drug-eluting stenting for unprotected left main coronary disease. *Circulation.* 2009;120:2214-2221.
192. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045-1057.
193. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357:2001-2015.
194. Mylotte D, Routledge H, Harb T, et al. Provisional side branch-stenting for coronary bifurcation lesions: evidence of improving procedural and clinical outcomes with contemporary techniques. *Catheter Cardiovasc Interv.* 2013;82:E437-E445.
195. Burzotta F, Gwon HC, Hahn JY, et al. Modified T-stenting with intentional protrusion of the side-branch stent within the main vessel stent to ensure ostial coverage and facilitate final kissing balloon: the T-stenting and small protrusion technique (TAP-stenting). Report of bench testing and first clinical Italian-Korean two-centre experience. *Catheter Cardiovasc Interv.* 2007;70:75-82.
196. Foin N, Sen S, Allegría E, et al. Maximal expansion capacity with current DES platforms: a critical factor for stent selection in the treatment of left main bifurcations? *EuroIntervention.* 2013;8:1315-1325.
197. Colombo A, Stankovic G, Orlic D, et al. Modified T-stenting technique with crushing for bifurcation lesions: immediate results and 30-day outcome. *Catheter Cardiovasc Interv.* 2003;60:145-151.
198. Colombo A. Balloon crush: new tool in bifurcation treatment armamentarium. *Catheter Cardiovasc Interv.* 2004;63:417-418.
199. Galassi AR, Colombo A, Buchbinder M, et al. Long-term outcomes of bifurcation lesions after implantation of drug-eluting stents with the "mini-crush technique." *Catheter Cardiovasc Interv.* 2007;69:976-983.
200. Furuichi S, Airolidi F, Colombo A. Rescue inverse crush: a way of get out of trouble. *Catheter Cardiovasc Interv.* 2007;70:708-712.
201. Chen S, Zhang J, Ye F, et al. DK crush (double-kissing and double-crush) technique for treatment of true coronary bifurcation lesions: illustration and comparison with classic crush. *J Invasive Cardiol.* 2007;19:189-193.
202. Siotia A, Morton AC, Malkin CJ, Raina T, Gunn J. Simultaneous kissing drug-eluting stents to treat unprotected left main stem bifurcation disease: medium term outcome in 150 consecutive patients. *EuroIntervention.* 2012;8:691-700.
203. Stinis CT, Hu SP, Price MJ, Teirstein PS. Three-year outcome of drug-eluting stent implantation for coronary artery bifurcation lesions. *Catheter Cardiovasc Interv.* 2010;75:309-314.



9 Chronic Total Coronary Occlusions: Rationale, Techniques, And Clinical Outcomes

DAVID E. KANDZARI, PRATIK B. SANDESARA AND WILLIAM J. NICHOLSON

INTRODUCTION, 159

INDICATIONS AND EVIDENCE, 159

Angina and Quality of Life, 160
Improvement in Left Ventricular Function, 160
Ventricular Arrhythmias, 161
Improved Tolerance of Ischemic Events, 161
Survival and Completeness of Revascularization, 161

ANATOMIC CONSIDERATIONS, 162

Histopathology of Chronic Total Occlusions, 162

Collaterals and Chronic Total Occlusions, 164
Target Vessel, 164

PROCEDURAL TECHNIQUES, 164

Vascular Access, Angiography, and Equipment Selection, 164
Guides, Guide Catheter Extensions, Guidewires, and Microcatheters, 166

TECHNICAL STRATEGIES, 167

Antegrade Techniques, 168
Antegrade Dissection and Reentry, 168

Retrograde Approach, 170

Hybrid Algorithm, 170

Imaging: Computed Tomography Angiography and Intravascular Ultrasonography, 170

COMPLICATIONS OF CTO PCI, 172

CONCLUSIONS, 172

INTRODUCTION

Since the first percutaneous transluminal coronary angioplasty by Andreas Gruentzig in 1977, significant advances in percutaneous coronary intervention (PCI) techniques have resulted in dramatically improved clinical outcomes over the past 4 decades.¹ However, chronic total occlusion (CTO) PCI represents a technically challenging subset and a clinical conundrum in contemporary interventional cardiology practice. CTOs are encountered in 15% to 30% of patients undergoing diagnostic coronary angiography.^{2,3} This prevalence increases to greater than 50% after coronary artery bypass grafting (CABG)²; studies have shown that CABG accelerates the progression of atherosclerosis in the native coronary arteries such that 43% of bypassed native arteries develop CTOs as early as 1 year after CABG.^{4,6} Despite the high prevalence, CTO PCI is attempted in fewer than 10% of cases, and the presence of a CTO is the most powerful predictor of incomplete revascularization (both with PCI and CABG surgery), referral for CABG surgery, and deferral to medical management.^{2,7-11} In the SYNTAX (SYNergy Between PCI with TAXUS and Cardiac Surgery) trial of multivessel PCI versus CABG surgery, the presence of a CTO was the most common reason for incomplete revascularization.¹¹ In this trial, the prevalence of CTO was 26% in the PCI compared with 40% in the CABG arm. Of the 266 patients with CTO randomized to CABG surgery, still only 68% received a bypass graft to the CTO vessel. This disparity in the prevalence of CTO and PCI highlights the technical challenges and complexities of CTO PCI as well as uncertainties about which patients may benefit from revascularization.^{12,13} Contrary to PCI for nonocclusive coronary artery disease, the preponderance of data on the efficacy of CTO PCI is derived primarily from observational studies and much more limited number of randomized controlled trials (RCTs).

INDICATIONS AND EVIDENCE

Patients with CTOs commonly present with symptomatic angina, and only about 10% to 15% remain asymptomatic.¹³⁻¹⁵ Atypical symptoms such as shortness of breath and fatigue may be more prominent than chest pain. Despite the presence of well-developed collaterals, the vast majority of patients with a CTO have demonstrable stress-induced ischemia on noninvasive testing.¹⁶⁻¹⁸ When a CTO is the only significant lesion, PCI can be considered in patients with the following three conditions: patient symptoms that can be attributed to the occluded vessel or in select cases of silent ischemia with large territory of myocardium at risk, the myocardial territory subtended by the CTO is viable, and the likelihood of success is moderate to high (>60%) with a low rate of major complications (<1% death and <5% myocardial infarction [MI]).¹⁹ CTO PCI based on these principles is congruent with the latest guideline recommendations in the United States and Europe.^{12,20} The 2011 American College of Cardiology/American Heart Association PCI guidelines provide a Class IIa, level of evidence B recommendation for CTO PCI in patients with appropriate clinical indication and suitable anatomy when performed by operators with appropriate expertise.¹² Similarly, the 2018 European Society of Cardiology/European Association of Cardio-Thoracic Surgery guidelines on myocardial revascularization CTO PCI has a Class IIa, level of evidence B recommendation with consideration of percutaneous CTO revascularization in patients with angina resistant to medical therapy or with a large area of ischemia in the target vessel territory.²⁰ Additionally, in the previous version of the Appropriate Use Criteria for Coronary Revascularization, different recommendations were provided for CTO versus non-CTO lesions, but this distinction has been eliminated from the most recent



guidelines, and indications for revascularization are provided irrespective of the presence of a CTO.^{21,22}

Although ischemic symptom improvement is the primary indication for CTO PCI, other potential clinical benefits may be achieved, including improvement in left ventricular (LV) function, ventricular arrhythmias, and survival in the setting of complete revascularization.²³

Angina and Quality of Life

Symptoms attributed to CTOs are indicators of myocardial ischemia.²⁴ Irrespective of collateral development, stress-induced ischemia can typically be elicited in most patients with CTOs, supporting the notion that collateral circulation is often insufficient to prevent stress-induced ischemia.^{16,17,25} Myocardium subtended by a CTO has often been described as a persistently ischemic zone, and the presence of inducible ischemia portends a worse prognosis.^{24,26} Observational studies show that CTO PCI is associated with improvement in myocardial perfusion and reduction in ischemic burden by noninvasive imaging.^{24,27-29} In 301 patients who underwent myocardial perfusion imaging before and after CTO PCI, a baseline ischemic burden of 12.5% was identified as the threshold for patients most likely to have a significant decrease in ischemic burden after CTO PCI, indicating that the benefits of CTO revascularization are likely to be achieved in patients with a significant baseline ischemic burden.²⁷ Observational studies and RCTs have shown symptom improvement after successful CTO PCI.³⁰⁻³⁵ In the OPEN-CTO (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion) registry of 1000 patients undergoing CTO PCI, significant improvements in validated health status outcomes (Seattle Angina Questionnaire [SAQ], Rose Dyspnea Scale score, and physician health questionnaire for depression score) were observed following successful CTO PCI at 1-month follow-up.³¹ Notably, patients with refractory angina who underwent successful CTO PCI experienced significant health status improvements, which persisted through 1-year follow-up.³⁶

The IMPACTOR-CTO trial (Impact on Inducible Myocardial Ischemia of Percutaneous Coronary Intervention versus Optimal Medical Therapy in Patients with Right Coronary Artery Chronic Total Occlusion) randomized 94 patients with isolated right coronary artery CTO to CTO PCI versus optimal medical therapy (OMT) at a single center and found greater ischemic burden reduction and improvement in quality of life and 6-minute walk distance in the CTO PCI group at 12 months.³⁰ Similarly, the EuroCTO (A Randomized Multicentre Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions) trial was a prospective, multicenter RCT of 396 patients randomized 2:1 to CTO PCI plus OMT versus OMT alone.³² The primary endpoint was change in health status assessed by the SAQ at baseline and 12-month follow-up. Greater improvements in angina frequency (5.23; 95% confidence interval [CI], 1.75–8.71; $P = .003$) and quality of life (6.62; 95% CI, 1.78–11.46; $P = 0.007$) were observed in the PCI group compared with the OMT group at 12 months. Additionally, improvement in physical limitation ($P = .02$) and complete

freedom from angina were more frequent with PCI than OMT alone (71.6% vs 57.8%; $P = .008$).

In a meta-analysis of six observational studies evaluating angina after CTO PCI, patients undergoing successful revascularization had a significant reduction in recurrent angina during a 6-year follow-up compared with patients undergoing unsuccessful PCI (odds ratio [OR], 0.45; 95% CI, 0.30–0.67).³⁴ Overall, strong data from both RCT and large observational studies have demonstrated benefits of CTO PCI in improving health status outcomes, including angina and quality of life metrics. Therefore, patients with medically refractory angina or moderate to large ischemic burden caused by a coronary CTO should be considered for revascularization.

Improvement in Left Ventricular Function

Chronic myocardial ischemia caused by decreased coronary blood flow can lead to repetitive stunning, hibernation, and fibrosis, which underlie the pathophysiology of impaired regional contractility, leading to LV systolic dysfunction in CTO patients.³⁷ Regional LV systolic function has been shown to improve after CTO PCI in observational studies.³⁸⁻⁴³ The degree of improvement is especially pronounced in patients with decreased LV systolic function at baseline, but no significant change expected with if LV function is normal.^{41,43} Notably, improvement in LV function is not predicted by a history of MI or duration of occlusion, and recovery of LV function is not related to the quality of collaterals present.⁴³ Two randomized trials were conducted to evaluate the improvement in LV function after CTO PCI versus OMT.⁴⁴ In the EXPLORE (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Elevation Myocardial Infarction) trial, 304 patients with ST-segment elevation myocardial infarction (STEMI) and a concurrent CTO in a non-infarct-related artery were randomized to CTO PCI within 1 week after revascularization of infarct related artery versus OMT did not show a difference in the mean left ventricular ejection fraction (LVEF) measured by cardiac magnetic resonance imaging (CMR) at 4 months between the two groups ($44.1 \pm 12.2\%$ vs $44.8 \pm 11.9\%$; $P = .60$).⁴⁴ Notably, the mean LVEF was not significantly reduced at baseline (41 ± 11 in the CTO PCI arm and 42 ± 12 in the OMT group). However, in the subset of patients with CTO in the left anterior descending coronary artery (LAD), there was improved LVEF in the CTO PCI arm compared with medical therapy ($47.2 \pm 12.3\%$ vs $40.4 \pm 11.9\%$; $P = .02$). In a substudy of the EXPLORE trial, CTO PCI was associated with greater recovery of regional systolic function in the dysfunctional segments (segmental wall thickening $<45\%$) with the most pronounced recovery in the dysfunctional but viable segments (transmural extent of infarction $\leq 50\%$).⁴⁵ The REVASC (Recovery of Left Ventricular Function After Stent Implantation in Chronic Total Occlusion of Coronary Arteries) trial evaluated the effect of CTO PCI on LV function assessed by CMR.⁴⁶ A total of 205 patients were randomized to CTO PCI versus medical management with CMR at baseline and at 6 months after intervention. At 6 months, no difference was seen in change in segmental wall thickening or LVEF between the two groups. The

baseline LVEF was greater than 50%, and there was no viability assessment in the study. Although both EXPLORE and REVASC failed to show a benefit of CTO revascularization on LV function compared with medical therapy, it is important to note that the limitations that patients in both studies had normal mean LVEF, and there was no assessment of viability at baseline. Given these limitations, these trials do not provide a definitive answer on whether CTO PCI improves LVEF. In general, the presence of ischemia and viability in the myocardium supplied by a CTO vessel should be assessed before consideration of revascularization in patients with ischemic cardiomyopathy and low LVEF to identify patients who are most likely to benefit.^{23,42,47,48}

Ventricular Arrhythmias

The presence of a CTO may predispose to ischemia-driven or scar-related arrhythmic events. Chronic hypoperfusion causing ischemia and scarring are postulated mechanisms for ventricular arrhythmias in patients with CTO. The VACTO (Ventricular Arrhythmias and Chronic Total Coronary Occlusion) study examined the impact of CTO on the incidence of appropriate implantable cardioverter-defibrillator (ICD) therapy for ventricular arrhythmias and mortality in patients with ischemic cardiomyopathy who underwent ICD implantation for primary prevention.⁴⁹ Among 162 patients with an ICD, 44% had at least one CTO, and appropriate ICD therapy was detected in 18% during a median follow-up of 26 months. The presence of a CTO was associated with higher ventricular arrhythmias and mortality. In multivariable analysis, the presence of a CTO was the strongest predictor (hazard ratio [HR], 3.5 [1.5–8.3]; $P = .003$) of appropriate ICD therapy. In patients with multivessel disease, those with a CTO had a higher occurrence of appropriate ICD therapy compared with those with multivessel disease but without a CTO. Like primary prevention, in recipients of ICD for secondary prevention, the presence of a CTO was associated with higher appropriate ICD therapies (51.7% vs 26.3%; $P = .001$) and mortality.⁵⁰ Further studies are needed to evaluate the impact of CTO PCI on reduction in ventricular arrhythmic events.

Improved Tolerance of Ischemic Events

The presence of a CTO in patients with high-risk acute coronary syndromes (ACSs) has been associated with adverse short- and late-term outcomes.^{51–55} Potential mechanisms include preexisting LV dysfunction, poor tolerance of ischemia secondary to limited collateral supply, and a “double jeopardy” phenomenon associated with simultaneous acute and chronic coronary occlusion in separate territories. Acute occlusion of the donor vessel in the presence of a CTO jeopardizes a much larger area of myocardium. In 3277 patients presenting with STEMI who underwent primary PCI, the presence of a CTO was a strong and independent predictor of 30-day mortality (HR, 3.6; 95% CI, 2.6–4.7; $P < .01$) compared with multivessel disease without a CTO (HR, 1.6; 95% CI, 1.2–2.2; $P = .01$).⁵³ Shock on presentation was the only greater predictor of death rather than the presence of a CTO. In a landmark analysis

including surviving patients from 30 days to 5 years, the presence of a CTO continued to be an independent predictor of death that exceeded the risk associated with single- or multivessel disease without CTO.

In the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) study of 3283 patients, 8.6% of patients had a non-infarct-related artery CTO.⁵² Like the prior study, a CTO in a non-infarct-related artery was an independent predictor of 30-day mortality (HR, 2.88; 95% CI, 1.41–5.88; $P = .04$) and late (30-day to 3-year) mortality (HR, 1.98, 95% CI, 1.19–3.29; $P = .009$). In contrast, multivessel disease without a CTO was associated with only 30-day mortality (HR, 2.20; 95% CI, 1.00–3.06; $P = .049$) but not late mortality. The TAPAS (Thrombus Aspiration in Percutaneous Coronary Intervention in Acute Myocardial Infarction) trial reported similar findings of a higher mortality rate in patients with CTO presenting with acute MI compared with non-CTO patients over a median follow-up of 2.1 years (HR, 2.41; 95% CI, 1.26–4.61; $P = .008$).⁵⁴

In a systematic review and meta-analysis of more than 14,000 patients, O'Connor et al.⁵⁵ evaluated the impact of the presence of a non-infarct-related artery CTO on short- and long-term mortality in patients presenting with STEMI treated with primary PCI. The presence of a non-infarct-related CTO was associated with an increased incidence of all-cause mortality compared with no CTO (absolute risk, 23.5% vs 9.0%; OR, 2.90; 95% CI, 2.09–4.01; $P < .0001$) at a median follow-up of 25 months.

Limited evidence exists to support attempted CTO revascularization after MI related to a non-CTO target vessel. One reason for the paucity of data on the benefit of nonculprit CTO revascularization is the exclusion of patients with CTO from several randomized studies evaluating complete revascularization versus culprit only revascularization in the setting of STEMI.^{56–58} As discussed earlier, the EXPLORE trial randomized patients to CTO PCI versus OMT in a non-infarct related artery within 1 week after primary PCI for STEMI. This trial did not show a significant improvement in LV function except for the subset of patients with LAD CTO and those with significant baseline dysfunctional segments by CMR.^{44,45}

Survival and Completeness of Revascularization

Observational studies and meta-analyses have consistently demonstrated reduction in mortality rate with CTO PCI compared with medical therapy.^{14,34,59} However, five randomized controlled clinical trials of CTO PCI versus no CTO PCI have been published to date with varying results, leading to controversy regarding the benefits on CTO PCI.^{30,32,44,46,60} The DECISION-CTO (Drug-Eluting Stent Implantation versus Optimal Medical Treatment in Patients with Chronic Total Occlusion) trial is the largest RCT of CTO PCI. It randomized 834 patients to CTO PCI versus no CTO PCI.⁶⁰ The overall success rate for CTO PCI was 91%. During a median follow-up of 4 years, there was no significant difference in the incidence of primary endpoint (composite of death, MI, stroke, and target vessel revascularization). Major limitations of the study need to be highlighted

and taken into consideration⁶¹: (1) the study was terminated before completion of enrollment of the planned 1284 patients because of slow recruitment, (2) almost 20% of patients in the non-CTO PCI arm crossed over to receive staged CTO PCI within 3 days of randomization, and (3) patients in both groups had multivessel disease and underwent revascularization for non-CTO lesions after randomization. This disparity between observational and randomized trial data is likely due to several challenges such as variability in operator experience, selection and treatment biases, management of patient cross-over, and intention to treat.

Several observational studies have compared outcomes in patients undergoing successful versus failed CTO PCI.^{33,34,62,63} Despite the nonrandomized study design, these studies have consistently demonstrated successful CTO revascularization is associated with improved survival but have inherent limitations such as ascertainment and selection bias. A meta-analysis of 25 studies with 28,486 patients showed CTO PCI success rate of 71%.³³ During a mean follow-up of 3.1 years, successful CTO PCI was associated with a lower mortality rate (OR, 0.52; 95% CI, 0.43–0.63), need for subsequent CABG (OR, 0.18; 95% CI, 0.14–0.22), and risk of major adverse cardiac events (0.59; 95% CI, 0.44–0.79) compared with failed CTO PCI.

Incomplete revascularization is associated with worse clinical outcomes compared with complete revascularization whether after bypass surgery or PCI, and the presence of a CTO is a major reason for incomplete revascularization.^{64,65} As angiographic disease complexity increases, completeness of revascularization measured by residual SYNTAX score paradoxically decreases.⁶⁶ The impact of CTOs on incomplete revascularization and its clinical implications were highlighted in the SYNTAX trial.¹¹ The prevalence rates of a CTO were 26.3% and 36.4% in the PCI and CABG groups, respectively. Almost 70% of all CTOs were localized to the proximal or midsegment of a major coronary artery—indicating at least moderate territory at ischemic risk—and the CTO PCI success rate was only 49.4%. Furthermore, the presence of a CTO was the strongest predictor of incomplete revascularization after PCI (HR, 2.70; 95% CI, 1.98–3.67; $P < 0.001$). Incomplete revascularization was associated with significant higher mortality rate and rate of major adverse cardiac events at 4-year follow-up, independent of treatment assignment to PCI or bypass surgery.

ANATOMIC CONSIDERATIONS

A CTO is defined as an occlusion with absence of antegrade flow (Thrombolysis in Myocardial Infarction [TIMI] grade 0 flow) through the lesion with a presumed or documented duration of 3 months or more.⁶⁷ The duration of coronary occlusion may be difficult to ascertain because serial angiograms are not always available and therefore it must be estimated from available clinical information such as clinical history of MI, change in angina pattern, and electrocardiographic changes.

Histopathology of Chronic Total Occlusions

Chronic coronary occlusions most commonly develop from thrombotic occlusion followed by thrombus organization and tissue aging. By histology, approximately half of all CTOs are less than 99% stenotic despite angiographically apparent total occlusion with TIMI grade 0 antegrade flow.⁶⁸ Histopathologically, a CTO is defined as a lumen area occupied by calcium, proteoglycan, or collagen, with or without neovascularization and chronic inflammation (Figure 9.1).⁶⁹ The concentration of collagen-rich fibrous tissue is particularly dense at the proximal and distal ends of the lesion, which contributes to a columnlike lesion of calcified, resistant fibrous tissue surrounding a softer core of organized thrombus and lipids.⁷⁰ Morphologically, long-duration CTOs predominantly include collagen and no fibrin in the matrix, whereas short-duration CTOs predominantly contain proteoglycan with fibrin in the matrix (Figure 9.2). CTO segments can be classified as “soft,” “hard,” or a mixture of both. Soft plaque consists of cholesterol-laden cells and foam cells with loose fibrous tissue and neovascular channels and is more characteristic of younger occlusions (<1 year old). On the other hand, hard plaque consists of dense fibrous tissue and large fibrocalcific regions without neovascular channels. Whereas soft plaque is more likely to allow wire passage either directly through tissue planes or via neovascular channels into the distal lumen, hard plaque is more likely to deflect coronary guidewires into the extra plaque space, creating dissection planes. Hard plaque is most common in post-CABG CTOs and in non-CABG with increasing CTO age (>1 year old). Although areas of calcification are present in CTOs before 3 months of age, the extent and severity of calcification increase with occlusion duration. The difficulty in

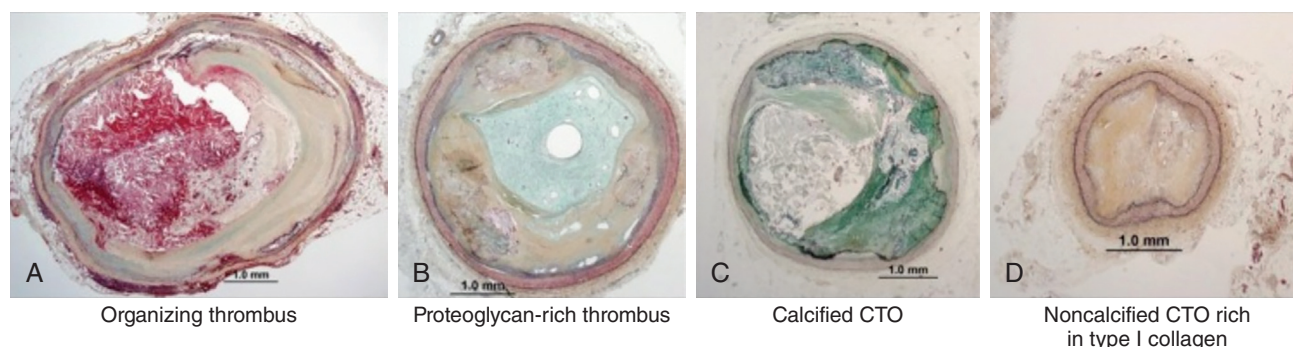


FIGURE 9.1 A–D, Representative images of the composition of various chronic total occlusions (CTOs). (Adapted from Sakakura K, Nakano M, Otsuka F, et al. Comparison of pathology of chronic total occlusion with and without coronary artery bypass graft. *Eur Heart J*. 2014;35:1683–1693.)

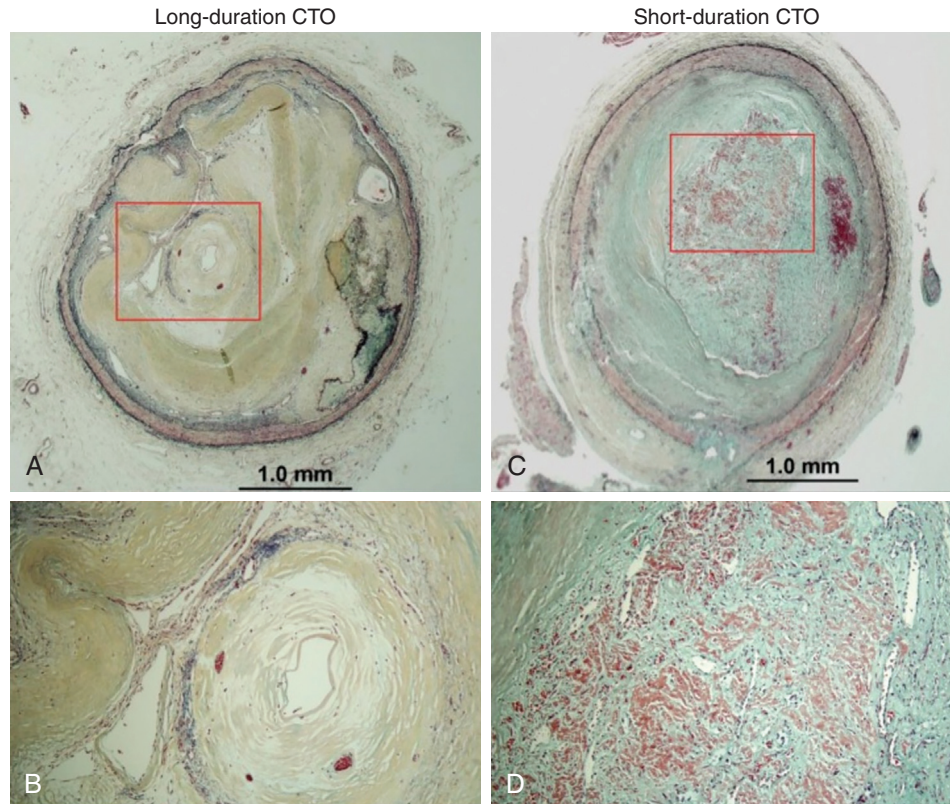


FIGURE 9.2 Histopathology specimen of a long-duration chronic total occlusion (CTO) (A) with predominantly collagen type I fibers in the matrix (B) and short-duration CTO (C) with predominantly proteoglycan and fibrin in the matrix (D). (Adapted from Sakakura K, Nakano M, Otsuka F, et al. Comparison of pathology of chronic total occlusion with and without coronary artery bypass graft. *Eur Heart J*. 2014;35:1683-1693.)

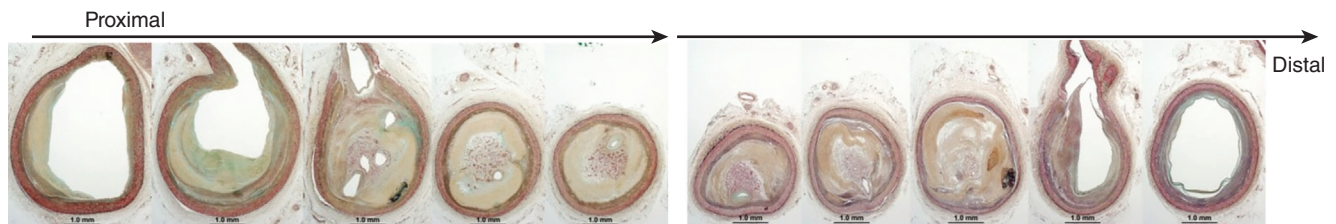


FIGURE 9.3 Long-duration chronic total occlusion (CTO) with severe negative remodeling. There is minimal calcification in the CTO segment. (Adapted from Sakakura K, Nakano M, Otsuka F, et al. Comparison of pathology of chronic total occlusion with and without coronary artery bypass graft. *Eur Heart J*. 2014;35:1683-1693.)

crossing older occlusions is likely attributable to this age-related increase in calcium and collagen content. Inflammatory cells are typically present in CTOs and consist of macrophages, foam cells, and lymphocytes. Inflammation is predominantly in the intima but can also exist in the media and adventitial layers of a CTO. With aging of fibrotic CTO lesions, the vessel frequently undergoes negative remodeling with a decrease in dimensions of the external elastic membrane caused by adventitial vascular responses. Infrequently, positive remodeling can occur because of plaque hemorrhage and inflammation. Longer duration CTOs exhibit more negative remodeling than shorter duration CTOs⁶⁹ (Figure 9.3). After successful CTO recanalization, this negative remodeling typically reverses with recovery of normal vessel dimensions on serial angiographic surveillance.⁷¹

Extensive neovascularization is often observed in the presence of CTOs with capillary density and angiogenesis increasing as the occlusion age increases. In CTOs less than 1 year in age, new capillary formation is greatest in

the adventitia and in CTOs of longer duration the size and number of capillaries in the intima increase to a similar or greater extent than those present in the adventitia. Angiogenesis within the CTO occurs early as relatively large (>250 μ m) capillaries are frequently present throughout the CTO vessel in young occlusions.

A rich neovascular network often traverses the CTO vessel wall, arising from the adventitial vasa vasorum across the media and into the lesion intima, suggesting that vessel in-growth proceeds from the adventitia in younger lesions. Autopsy studies of subtotally occluded atherosclerotic lesions showed that new intimal vessels originate in the adventitial vasa vasorum in stenosed segments but rarely from the coronary lumen.⁷² These microchannels, which can recanalize the distal lumen, may result from thrombus-derived angiogenic stimuli and are suggestive of an old CTO, often without a well-defined proximal cap or stump on angiogram. Therefore, the distinction should be made between ipsilateral epicardial angiographic “bridging” collateral vessels and true microvascular collaterals.



Neochannels may also develop with organization of thrombus, connecting the proximal and distal lumens; this is suggested by a tapered CTO proximal cap on angiogram. Such channels may serve as a route for a guidewire to reach the distal vessel. More than half of the proximal caps are abrupt (blunt), and more than 70% of the distal caps are tapered.⁶⁹ Furthermore, post-CABG and long-duration CTOs are more likely to have a blunt or abrupt proximal cap compared with the distal cap.

The pathology of CTOs can be summarized as follows⁶⁹: (1) CTOs after CABG are characterized by severe calcification and therefore have only mild to moderate negative remodeling; (2) longer duration CTOs without a history of CABG are characterized by moderate calcification and severe negative remodeling; (3) short-duration CTOs without a history of CABG are characterized by minimal calcification and more organized thrombi and necrotic core and the least negative remodeling; (4) a proximal cap is more frequently blunt than a distal cap, which is more commonly tapered; and (5) a blunt proximal cap is most commonly seen in post-CABG CTOs.

Collaterals and Chronic Total Occlusions

Collaterals are interarterial connections that preserve myocardial function and prevent myocardial necrosis in myocardial territory supplied by a CTO. The most widely used angiographic grading system, described by Rentrop et al.,⁷³ does not actually characterize the collaterals themselves but rather their contribution to filling the occluded arterial segment (Table 9.1).³ Werner developed another grading of collateral connections specifically for CTOs to assist in interventional decision making regarding retrograde strategies (Table 9.2 and Figure 9.4).⁷⁴⁻⁷⁶ Collaterals develop in the setting of a pressure gradient (demand) and anatomy.⁷⁵ Common collateral patterns observed on coronary angiograms from 418 patients with 519 CTOs for the

right coronary artery (RCA), left LAD, and left circumflex coronary artery (LCX) are shown in Figure 9.5.⁷⁷

Even well-developed collaterals do not prevent ischemia during exercise.⁷⁸ A total occlusion that is well collateralized is functionally equivalent to a 90% stenosis in a non-CTO vessel.⁷⁹ After initial CTO crossing before recanalization, fractional flow reserve (FFR) values were universally ischemic (resting distal coronary pressure to aortic pressure ratio [Pd/Pa] < 0.80), and resting ischemia was present in 78% of instances.²⁵ Ischemia was demonstrated in all CTO cases independent of collateral development or presence of severe regional LV dysfunction. The myocardium remains viable but becomes ischemic during periods of increased oxygen demand, so patients with these lesions are likely to have exertional angina or dyspnea. Although risk of spontaneous ACS caused by a chronically occluded lesion is unlikely, infarction in the distribution of the CTO may result during instances of increased demand or if the arteries supplying the collaterals become compromised in any way.

Target Vessel

There is minimal data on the potential for differential benefit of CTO recanalization based on the target vessel (i.e., LAD, LCX, or RCA). In a large single-center registry, CTO PCI of the LAD but not LCX or RCA was associated with improved long-term survival.⁸⁰ Among 2608 patients, the LAD, LCX, and RCA were the target vessel in 936 (36%), 682 (26%), and 990 (38%) cases, respectively. Angiographic success rates were similar across the three coronary artery distributions (LAD, 77%; LCX, 76%; RCA, 72%). Procedural success compared with failure was associated with improved 5-year survival in the LAD (88.9% vs 80.2%; $P < .001$) group only and not in the LCX (86.1% vs 82.1%; $P = 0.21$) or RCA (87.7% vs 84.9%; $P = .23$) groups. In multivariable analysis, CTO PCI success in the LAD cohort was associated with decreased mortality (HR, 0.61; 95% CI, 0.42–0.89).

Various scoring systems have also been developed to predict the likelihood of successful CTO PCI.⁸¹⁻⁸³ The J-CTO (Multicenter CTO Registry in Japan) score was developed to assess successful guidewire crossing within 30 minutes based on five criteria (blunt stump, occlusion length >20 mm, intralumenal bending ≥ 45 degrees, mild to moderate calcification, and previous failed CTO attempt).⁸¹ One point is assigned for presence of each of the five criteria, enabling stratification into easy, intermediate, difficult, and very difficult groups to indicate the probability of guidewire crossing within 30 minutes. This has been validated in other cohorts.⁸⁴

PROCEDURAL TECHNIQUES

Vascular Access, Angiography, and Equipment Selection

Decisions regarding femoral or radial vascular access are typically made according to operator preference with consideration of patient-specific factors that may mandate one or the other approach. Although femoral access facilitates larger and possibly more supportive guiding catheters that can accommodate simultaneous use of multiple devices, this approach carries a higher risk for vascular

TABLE 9.1 Angiographic Definition of Chronic Total Occlusion Collateral Supply

RENTOP CLASSIFICATION GRADING OF COLLATERAL FILLING	DESCRIPTION
0	No visible filling of any collateral channels
1	Filling of collateral vessels without any epicardial filling of the target artery
2	Partial epicardial filling by collateral vessels of the target artery
3	Complete epicardial filling by collateral vessels of the target artery

TABLE 9.2 Werner Collateral Classification

COLLATERAL CONNECTION GRADE	DESCRIPTION
CC 0	No continuous connection
CC 1	Threadlike continuous connection
CC 2	Side branchlike connection (≥ 0.4 mm)
CC 3	>1 mm diameter of direct connection (not included in the original description)

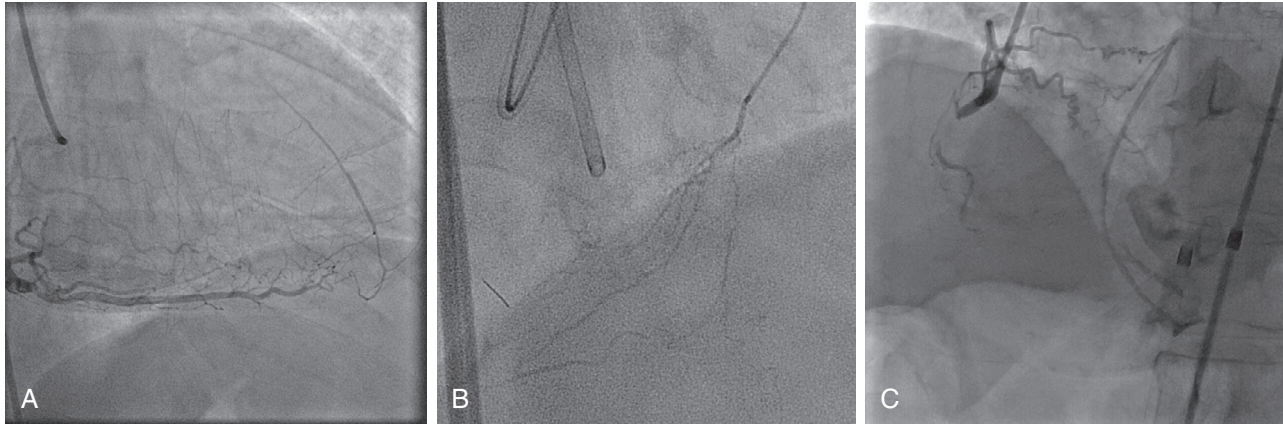


FIGURE 9.4 Coronary collateral circulation to chronic total occlusions. Angiographic examples of septal (**A** and **B**) and epicardial (**C**) collateral circulation. **B**, Microcatheter selective contrast injection into a septal collateral to the distal right coronary artery. Collaterals may be graded as grade 0, no continuous connection between donor and recipient artery; grade 1, continuous, threadlike connection; and grade 2, continuous, small, side branchlike size of the collateral throughout its course. (Reproduced from Surmely JF, Katoh O, Tsuchikane E, et al. Coronary septal collaterals as an access for the retrograde approach in the percutaneous treatment of coronary chronic total occlusions. *Catheter Cardiovasc Interv.* 2007;69:826-832.)

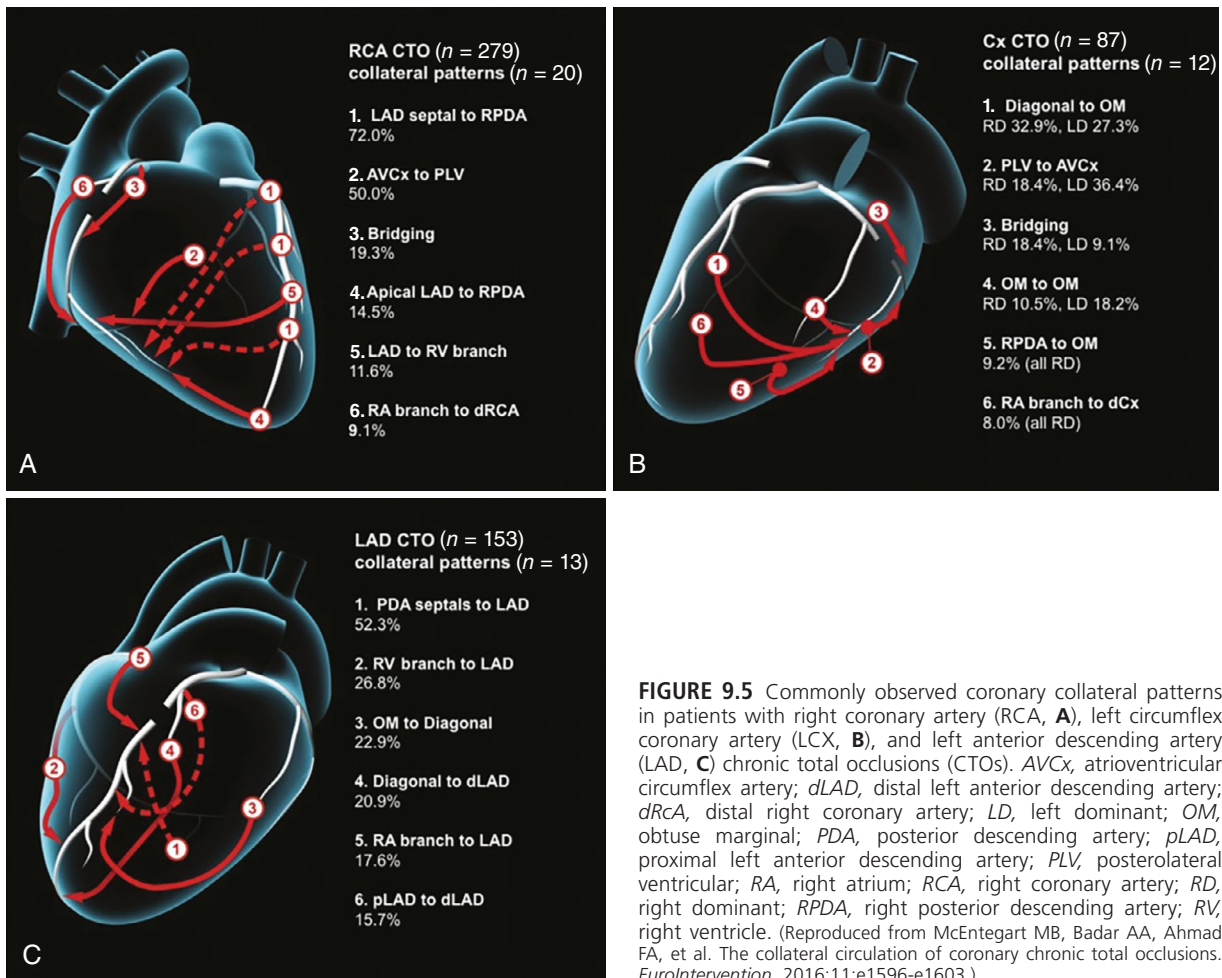


FIGURE 9.5 Commonly observed coronary collateral patterns in patients with right coronary artery (RCA, **A**), left circumflex coronary artery (LCX, **B**), and left anterior descending artery (LAD, **C**) chronic total occlusions (CTOs). AVCx, atrioventricular circumflex artery; dLAD, distal left anterior descending artery; dRCA, distal right coronary artery; LD, left dominant; OM, obtuse marginal; PDA, posterior descending artery; pLAD, proximal left anterior descending artery; PLV, posterolateral ventricular; RA, right atrium; RCA, right coronary artery; RD, right dominant; RPDA, right posterior descending artery; RV, right ventricle. (Reproduced from McEntegart MB, Badar AA, Ahmad FA, et al. The collateral circulation of coronary chronic total occlusions. *EuroIntervention.* 2016;11:e1596-e1603.)

complications than a radial approach.⁸⁵ A large systematic review and meta-analysis comparing radial versus femoral access in CTO PCI showed radial access was used in less complex lesions than femoral access but was associated with similar technical success rates and lower risk of access site complications and major bleeding.⁸⁶

Selection of guide catheters is limited by the choice of vascular access. A transradial approach can typically accommodate 6- or 7-Fr and occasionally sheathless 8-Fr guide catheters⁸⁷ compared with 6- to 8-Fr caliber sheaths and guides used in transfemoral CTO PCI. Dual arterial access is important for most CTO PCI approaches. This



can include radial-femoral, biradial, or bifemoral access. For femoral access, use of long (45 cm) sheaths is recommended for increased passive support. Optimal guide catheter support and coaxial alignment are also essential before guidewire engagement. When using femoral access, fluoroscopy- and ultrasound-guided access is paramount to minimize risk of complications.

Performing diagnostic angiography and its interpretation is essential for procedural planning and success. Dual coronary angiography helps identify accurate CTO length, delineates collateral filling, identifies the proximal and distal CTO caps, and provides optimal CTO segment visualization. It also helps visualize guidewire location during crossing attempts and helps manage periprocedural complications such as perforations.²³ Key principles of optimal angiography include prolonged image acquisition without table panning at low magnification from multiple orthogonal views to allow for optimal visualization of the CTO segment and collateral supply. Even when only ipsilateral collateral supply exists, impaired antegrade flow after attempted recanalization may result in preferential collateral shift to retrograde channels otherwise initially inapparent. **Table 9.3** outlines optimal angiographic projections for RCA, LAD, and LCX CTO to visualize proximal caps, distal landing zones, and collaterals.⁸⁸ Careful review of multiple angiographic projections is recommended to improve technical success and minimize complications. Ad hoc CTO PCI is strongly discouraged to allow adequate procedure planning and proper counseling of patients.²³

TABLE 9.3 Optimal Angiographic Projections to Visualize Proximal Cap, Collaterals, and Distal Vessels

VESSEL	ANGIOGRAPHIC PROJECTION
RCA	• LAO 30, AP 0: visualize proximal cap and ipsilateral collaterals from conus or RV marginal branches • LAO 30, cranial 20–30: visualize distal bifurcation and landing zones for ADR • RAO 30, cranial 10: visualize septal collaterals from the LAD • LAO 30, cranial 20–30: visualize collaterals from LCX traversing the AV groove • RAO 30: distinguish RCA from RV marginal branches
LAD	• RAO 0, cranial 30: visualize the proximal cap, lesion length, and distal landing zone • LAO 0–30, caudal 30: visualize proximal or ostial LAD CTO cap • RAO 30, cranial 0–30: visualize septal collaterals from the PDA and RV marginal branch and ipsilateral proximal to distal LAD septal collaterals • LAO 30, cranial 30: visualize ipsilateral connections from proximal to distal diagonals • LAO 30, cranial 0: visualize collaterals from the proximal RCA via conus branches
LCX	• LAO 0–30, caudal 30: visualize the proximal cap • LAO 30, cranial 30: visualize collaterals from the PLV branch of the RCA to AV groove LCx and diagonal to marginal collaterals • RAO 30, cranial 0: visualize collaterals from PDA to the marginal branches of the LCX • RAO 0, caudal 30: visualize collaterals from the proximal marginal branches to distal marginal branches

ADR, Antegrade dissection and reentry; AP, Antero-posterior; CTO, chronic total occlusion; LA, left atrial; LAD, left anterior descending coronary artery; LAO, left anterior oblique; LCX, left circumflex coronary artery; PDA, posterior descending artery; PLV, posterior left ventricular artery; RAO, right anterior oblique; RCA, right coronary artery; RV, right ventricular.

Unfractionated heparin (UFH) is the preferred antithrombin therapy during CTO PCI procedures. In rare cases of hemodynamically significant perforation, the drug can be reversed with protamine. Use of direct thrombin inhibitors and low-molecular-weight heparins is discouraged because of anecdotal reports of donor vessel thrombosis during retrograde PCI and the inability of immediate reversal of the anticoagulant effect.⁸⁹ UFH also allows for precise assessment and titration of antithrombin effect during the procedure. For antegrade and retrograde CTO PCI, activated clotting times (ACTs) of greater than 300 seconds and greater than 350 seconds, respectively, are recommended. The reason for more intensive anticoagulation for retrograde CTO PCI is the prevention of donor vessel thrombosis. Frequent measurement of the ACT (at least every 30 minutes) is recommended. Preprocedural administration of aspirin and thienopyridine therapy is recommended. Treatment with glycoprotein IIb/IIIa inhibition is rarely advocated except in the rare instances of coronary thrombosis refractory to therapeutic antithrombin therapy.

Guides, Guide Catheter Extensions, Guidewires, and Microcatheters

Strong guide catheter support is essential for successful CTO PCI. Femoral access, and 7- or 8-Fr guide catheters may provide more passive support. Typically for the RCA, Amplatz left guide catheter (AL 1 or AL 0.75) from radial or femoral access and three-dimensional (3D) right guide catheters from radial access provide adequate support. In particular, the 3D right guide catheter allows for deep engagement with clockwise rotation. Typically, EBU or XB guides are used for the left coronary artery from radial or femoral access because they provide a high degree of support. In addition, guide catheter extensions provide not only advanced support for guidewire crossing but also enable device delivery and exchange, and in some instances facilitate retrograde guidewire recanalization. As a unique guide extension design, a purpose-built guide catheter extension (TrapLiner, Teleflex) also permits device exchange over a 180- to 190-cm guidewire without the need for guidewire exchange, guidewire extension, or introduction of an additional trapping angioplasty balloon within the guiding catheter.⁹⁰

Crossing the CTO segment with a guidewire is the most important and challenging aspect of CTO PCI and the most common cause of failed intervention. Successful CTO recanalization involves penetrating the proximal fibrous cap, traversing the body of the CTO to reach the distal cap, penetrating the distal fibrous cap, or wiring collaterals. Significant advancements in coronary guidewire technology with distinct wire characteristics help navigate challenges of CTO recanalization. CTO guidewires can be divided into two major groups: (1) polymer-coated (hydrophilic or lubricious) guidewires and (2) stiffer, nonpolymer- (nonhydrophilic, hydrophobic, or nonlubricious) coated guidewires. Several polymer-coated wires are designed with a tapered (e.g., 0.009- to 0.010-inch) tip. Polymer-coated wires are used to navigate tortuosity and track tissue within the CTO segment with a low risk of vessel exit. These wires are particularly useful as “knuckle” wires and

are often used as first line antegrade wires. Stiffer nonpolymer-coated wires can be used to navigate the CTO body, and the high-gram-tip load wires can be used to penetrate resistant proximal or distal CTO caps. Dedicated collateral crossing wires with low tip load and high torque ability can be used to cross collateral channels. After successful retrograde CTO crossing, specially designed externalization wires can be used. Recent studies examining the effectiveness of specialized guidewires for CTO PCI have reported some of the highest rates of guidewire crossing success.^{90,91} Examples of available specialty CTO wires according to desired wire function for CTO PCI are listed in Table 9.4.⁹²

A microcatheter should be used for support and rapid guidewire exchange during CTO PCI.²³ They improve guidewire movements and alter the penetration force of the guidewire by changing the distance between the tip and the guidewire. Furthermore, they dilate collateral channels and can be used to facilitate selective delivery of contrast media for visualization. Microcatheter designs have been further modified to match a specific objective such as navigation through tortuous or small caliber collateral channels or crossing through calcified, resistant occlusive plaque. Although over-the-wire balloons were used in the past for similar function, they are not routinely used in contemporary CTO PCI. Several different types of microcatheters are available to meet specific challenges of CTO PCI and can be grouped into the following categories: (1)

braided (non-coil-based) microcatheters, (2) coil-based microcatheters, (3) penetration microcatheters, (4) directional microcatheters, and (5) dual-lumen microcatheters.

TECHNICAL STRATEGIES

Specialized coronary guidewires, microcatheters, and guide extension catheters are the key instruments in the contemporary CTO toolbox. In addition to the advancements in CTO-specific guidewire technology, significant advancements have occurred with strategies and technical skills regarding the use of these tools to improve procedural and clinical outcomes.

After dual coronary angiography, four characteristics of the CTO anatomy (Figure 9.6) should be assessed to determine optimal strategy for CTO PCI: (1) proximal cap location and morphology; (2) occlusion length, course, and composition, including calcification; (3) quality of the distal vessel; and (4) characteristics of collateral circulation.^{23,93} These four angiographic characteristics form the basis for the hybrid algorithm and dictate the initial procedural approach.⁹³ *Proximal cap morphology* refers to presence of an ambiguous cap and whether the ambiguity can be resolved with the use of tools such as intravascular ultrasonography (IVUS) or coronary computed tomography angiography (CCTA). A retrograde approach is recommended as the primary strategy in cases of an ambiguous proximal cap. CTO lesion length 20 mm or longer is associated with lower success rates and longer procedure times with standard antegrade wire escalation so that early adoption of alternative techniques may be necessary.⁸¹ Similarly, severe calcification or tortuosity within the CTO segment are important factors to consider. A large-caliber distal vessel with adequate visualization facilitates CTO recanalization compared with negatively modeled, small-diameter distal vessels.²³ Evaluation of size and suitability of collaterals for a retrograde approach should be assessed.

TABLE 9.4 Chronic Total Occlusion Guidewires and Characteristics

CTO FUNCTION	PROPERTIES	EXAMPLES
Collateral crossing	Flexible body with excellent torque control and trackability	- Suoh 3/Sion/Sion black/Fielder XT-R (ASAHI Intecc) - Samurai RC (Boston Scientific)
Loose tissue tracking	Jacketed or nonjacketed Tapered tip Low tip load Low penetration force	- Pilot 50 (Abbott Vascular) - Fielder XT family (Asahi Intecc) - Fighter (Boston Scientific)
Lesion crossing	Low to medium tip load (1–6 g) Jacketed or nonjacketed	- Pilot 200 (Abbott Vascular) - Gaia family, Gladius (Asahi Intecc) - Judo family (Boston Scientific)
Knuckling	Jacketed	- Pilot 200 (Abbott Vascular) - Fielder XT (ASAHI Intecc) - Fighter (Boston Scientific) - Gladius Mongo (ASAHI Intecc)
Dissection reentry	High penetration force	- Confianza Pro 12, Astato 20 (ASAHI Intecc) - Hornet 14 (Boston Scientific) - Stingray wire (Boston Scientific)
Penetration of resistant proximal and cap	High tip load	- Confianza Pro 12 (ASAHI Intecc) - Hornet 14 (Boston Scientific)
Externalization	>300-cm length	- RG3 (ASAHI Intecc) - R350 (Vascular Solutions)

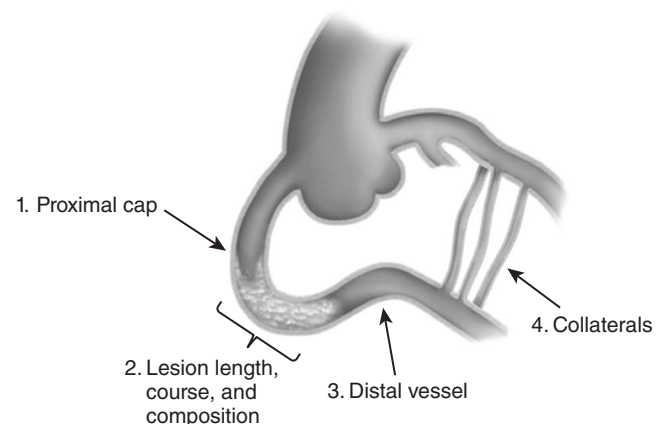


FIGURE 9.6 Four angiographic characteristics of the chronic total occlusion (CTO) anatomy should be assessed with dual coronary angiography to determine optimal strategy for CTO recanalization. (1) proximal cap morphology; (2) lesion length, course, and composition such as calcification; (3) distal vessel quality; ; (4) characteristics of collateral circulation. (Reproduced from Brilakis ES, Mashayekhi K, Tsuchikane E, et al. Guiding principles for chronic total occlusion percutaneous coronary intervention. *Circulation*. 2019;140:420-433.)

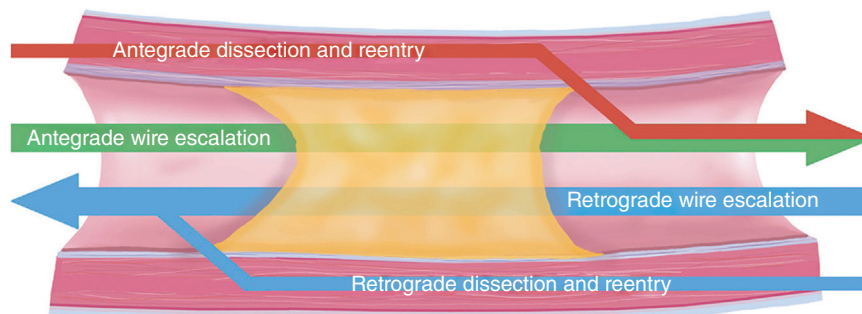


FIGURE 9.7 Contemporary chronic total occlusion crossing strategies include antegrade wiring, antegrade dissection and reentry, retrograde wiring, and retrograde dissection and reentry. (Adapted from Maeremans J, Walsh S, Knaepen P, et al. The hybrid algorithm for treating chronic total occlusions in europe: the RE-CHARGE Registry. *J Am Coll Cardiol*. 2016;68:1958-1970.)

Four CTO crossing strategies are used in current practice (Figure 9.7): (1) antegrade wiring, (2) antegrade dissection and reentry (ADR), (3) retrograde wiring, and (4) retrograde dissection and reentry.²³

Antegrade Techniques

The antegrade approach is the most common initial strategy for attempting CTO recanalization.^{94,95} Antegrade wire escalation (AWE) should be attempted in the presence of a tapered, nonambiguous proximal cap, occlusion length less than 20 mm, and a well-defined distal target vessel. Typically, a microcatheter with either a stiff, nonhydrophilic guidewire or a tapered or nontapered hydrophilic wire is used to drill and probe the lesion initially. If the proximal cap is tapered or a visible channel is present, a tapered, polymer-jacketed, low-gram-tip load guidewire can be used initially. For blunt proximal caps, an intermediate penetration force polymer-jacketed wire or composite core guidewire should be the initial choice. Progressively stiffer wires (“guidewire escalation”) can be used if the proximal cap cannot be penetrated or the initial wire is unable to be advanced within the lesion. Wire shaping for antegrade CTOs is different than for nonocclusive disease. The initial wire should have a bend with an angle less than 30 degree approximately 1 mm from the tip. If more angulated bends are required to access the CTO segment, this should be done with a soft, floppy wire and then exchanged for a CTO wire to avoid proximal vessel trauma from free passage of the CTO wire.

In two large registries, AWE was the final crossing strategy in more than half of cases and was typically used for less complex lesions.^{94,95} Two specialized techniques for recanalization of CTOs with an antegrade approach can be used after failure of the initial wire’s entry into the true lumen. The parallel wire technique that involves leaving the guidewire in place (often in the subintimal space) and directing a second guidewire into the distal true lumen often with the use of dual lumen microcatheters, or the use of ADR.

The subintimal tracking and reentry (STAR) technique is a method of intentional subintimal dissection using a hydrophilic wire typically shaped with a prolapsed tip.⁹⁶ The wire is advanced beyond the occlusion adjacent to the distal true lumen. The looped “knuckle wire” follows the subintimal path to a point where the dissection can no

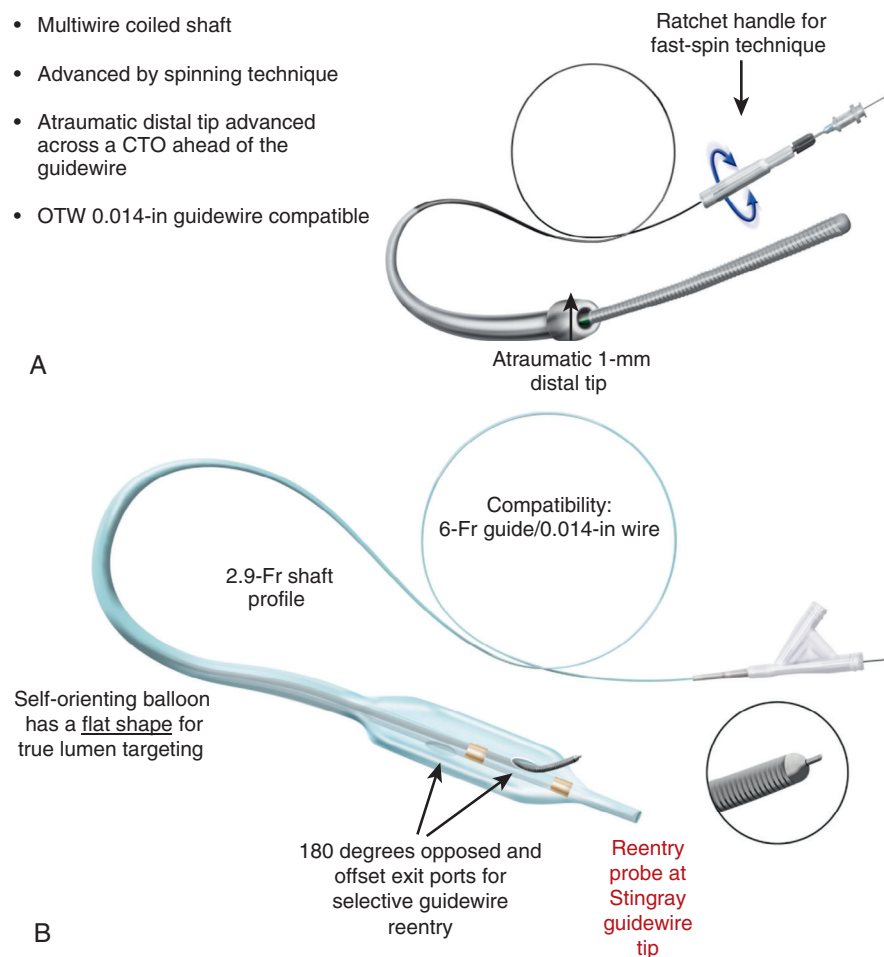
longer be propagated and may spontaneously reenter the true lumen in the main vessel, which typically occurs at a distal bifurcation. Ultimately, an extensive dissection is created that may need to be treated with extensive stenting or alternatively with angioplasty alone to permit vessel healing followed by selective stent placement weeks later (“investment procedure”).^{97,98} This method can result in pruning and occlusion of side branches and higher rates of restenosis and is therefore reserved as a bailout technique for highly symptomatic patients refractory to medical therapy after exhaustion of other recanalization strategies.⁹⁹ In recent years, STAR has reemerged as a technique for revascularization in the setting of poor distal vessel visualization or absence of collaterals and as a bailout strategy when other approaches fail.⁹⁹ Although contemporary STAR technique has evolved to minimize dissection, improve outflow, and leverage IVUS-guided deferred stenting, further studies are needed with long-term clinical follow-up.⁹⁹

Antegrade Dissection and Reentry

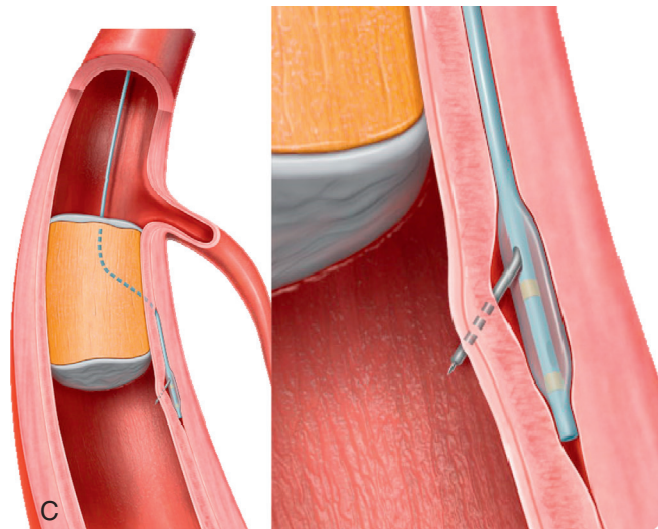
The primary mode of failure to recanalize a chronically occluded vessel is intentional or unintentional entry of the guidewire into the subintimal space with an inability to reenter the distal true lumen. Technological advances with dedicated reentry devices enable more predictable lumen reentry reducing the need for retrograde bailout strategies and thus leading to increased procedural success.^{100,101} The current system consists of the Crossboss support catheter, Stingray balloon, and Stingray reentry guidewire (Bridgepoint Medical/Boston Scientific) (Figure 9.8). The Crossboss catheter is a metal-braided, over-the-wire support catheter with a 1-mm rounded distal tip that can support standard guidewire manipulation or can be advanced using rapid rotation with or without the wire leading. Without the wire leading, the catheter may cross independently into the distal true lumen or enter the subintimal space, permitting setup for the Stingray reentry system. When distal to the occluded segment, it is important to not advance the Crossboss catheter or subintimal guidewire distally because this can lead to further dissection propagation and hematoma formation, which will compress the distal lumen. Controlled reentry can be attempted with the Stingray system at this point. The Stingray balloon is a 1-mm-thick, over-the-wire balloon catheter with three exit

- Multiwire coiled shaft
- Advanced by spinning technique
- Atraumatic distal tip advanced across a CTO ahead of the guidewire
- OTW 0.014-in guidewire compatible

A



B



C

FIGURE 9.8 Stingray balloon and Stingray reentry guidewire. The Crossboss catheter (A) is a metal-braided, over-the-wire support catheter with a 1-mm rounded distal tip that can support standard guidewire manipulation or can be advanced using rapid rotation with or without the wire leading. The Stingray balloon (B) is an over-the-wire balloon catheter with three exit ports (one distal and two 180-degree diametrically opposed sideports). When the balloon is inflated, it contours the artery with one exit port always directed to the adventitia (C) and one always directed toward the lumen, permitting advancement of a specialized guidewire to enter the true lumen space. CTO, Chronic total occlusion; OTW, over the wire.

ports (one distal and two 180-degree diametrically opposed sideports) (see Figure 9.8). After being inflated, the balloon contours the artery with one exit port directed toward the adventitia and one directed toward the vessel lumen (180 degrees opposite each other). Under fluoroscopy and applying orthogonal views, the operator can

select the lumen port with either the dedicated Stingray reentry wire or different high gram tip load wire to pierce the thin intimal tissue and reenter the distal true lumen. The targeted reentry is intended to limit dissection extent and preservation of side branches. ADR has been shown to be effective, especially for recanalization of more complex



CTO lesions with favorable outcomes.¹⁰¹⁻¹⁰³ The efficacy of dissection and reentry technique was illustrated elegantly in a study comparing outcomes after CTO PCI with dissection and reentry techniques (DART) and subintimal stenting versus intimal (i.e., intraplaque) techniques.¹⁰³ At 12 months, no adverse effects on intravascular healing using optical coherence tomography were noted for patients treated with DART compared with those treated with intimal techniques. Additionally, the crossing strategy was not an independent predictor of target vessel failure at 12 months.

Retrograde Approach

Despite advances in antegrade techniques, a retrograde approach may be necessary for anatomically complex CTO lesions. The retrograde approach involves advancing a guidewire through collateral channels into the distal true lumen followed by attempted CTO segment crossing using retrograde wire escalation, controlled antegrade and retrograde subintimal tracking (CART) or reverse CART.¹⁰⁴ In 2006, Surmely et al.¹⁰⁵ pioneered the modern era of retrograde CTO recanalization after reporting retrograde crossing via septal collaterals. The retrograde approach has been increasingly used and has led to increased CTO PCI success rates from around 70% to 90% in recent years.^{94,95,106,107} The contemporary retrograde approach includes septal and epicardial collaterals and aortocoronary bypass grafts as conduits.¹⁰⁸ Collaterals typically originate from contralateral coronary artery; therefore, dual access is required. Typically, shorter retrograde or “donor” guide catheter (85–90 cm) are essential to enable the retrograde microcatheter to reach the antegrade guide catheter. Selective angiography of the collateral to assess size, tortuosity, angle of entry to and exit, bifurcations, and distance from the collateral exit to distal cap can be helpful.¹⁰⁴ After a collateral is localized, crossing can be attempted with a soft nontraumatic wire (see Table 9.4) and microcatheter. After successful retrograde crossing with the guidewire and microcatheter, various CTO crossing techniques can be performed. Retrograde wire escalation can be attempted for short occlusions (<20 mm) with a tapered distal cap. Primary retrograde crossing is successful in less than 70% of attempts.⁹⁵ When the primary retrograde crossing attempt fails, variations on the retrograde approach include controlled dissection techniques such as CART and reverse CART (Figure 9.9). When antegrade and retrograde guidewires are used to cross a CTO, the guidewires typically will reside with four locations relative to one another: (1) antegrade intraplaque/retrograde intraplaque, (2) antegrade intraplaque/retrograde false lumen, (3) antegrade false lumen/retrograde intraplaque, and (4) antegrade false lumen/retrograde false lumen. The reverse CART method is more commonly used because it avoids delivery of balloon catheters through collateral channels. With reverse CART, a balloon is inflated in the proximal segment of the CTO over the antegrade wire that is in the false lumen. A retrograde guidewire is introduced past the distal cap of the CTO and into the subintimal space. When the antegrade balloon is inflated, expanding the subintimal space, the retrograde wire is then directed

toward the antegrade balloon, and when the retrograde wire enters the space occupied by the balloon, it may then be advanced proximally into the true lumen parallel to the path taken by the antegrade guidewire and balloon. In cases of failed connection, larger antegrade balloons can be used. Guide catheter extensions can also be used to help facilitate reverse CART. After successful crossing, wire externalization is performed using two currently available externalization wires (see Table 9.4). CART is the same concept, although the roles are reversed; specifically, a balloon is inflated in the distal portion of the CTO on the retrograde wire, and the antegrade wire is advanced from the subintimal space into the distal true lumen.

Compared with antegrade techniques, the retrograde approach has a higher risk of complications and therefore should be used in carefully selected patients.^{94,106,109} Potential complications of retrograde CTO PCI include collateral channel perforation, donor vessel complications such as thrombosis or guide-induced dissection, periprocedural MI, vascular access complications, and death (Figure 9.10).^{94,104} Use of a retrograde approach was associated with a higher risk of procedural-related death than the antegrade approach (1.50% vs 0.36%; $P = .017$).⁹⁴

Hybrid Algorithm

Selection of the optimal initial and subsequent crossing strategy (antegrade or retrograde approach) depends on the anatomy defined by dual angiography. The hybrid algorithm (Figure 9.11) was proposed to explore sequential options through an algorithm-based approach to shorten procedure time, minimize contrast and radiation use, standardize procedural strategy, and improve procedural success.⁹³ The hybrid method limits variability among operators regarding technique and strategy by standardizing the approach to CTO PCI based on four lesion characteristics: (1) lesion length longer than 20 mm, (2) proximal CTO cap ambiguity, (3) presence of interventional collaterals, and (4) suitability of the distal vessel for targeted reentry. The hybrid algorithm has been demonstrated to achieve CTO PCI success rates that exceed 90% overall and may be associated with a higher success rate than more traditional methods in more complex (e.g., J-CTO score ≥ 3) lesions.^{94,95}

Imaging: Computed Tomography Angiography and Intravascular Ultrasonography

Characterization of the plaque (i.e., calcification) and visualization of the distal vessel are important before attempted recanalization of a CTO. This is usually done with invasive angiography using contralateral injection of contrast into the artery supplying collaterals to the distal vessel. However, if there is doubt regarding the location of vessel anatomy, especially within the occluded segment, CCTA with 3D reconstruction can be helpful. Imaging with CCTA may improve patient selection for CTO recanalization, resolve proximal cap ambiguity, reduce the time and contrast needed for the procedure, decrease complications, and ultimately improve outcomes.^{110,111} Developments with coregistration algorithms that integrate 3D CCTA and two-dimensional fluoroscopy images may facilitate the procedural success of CTO by

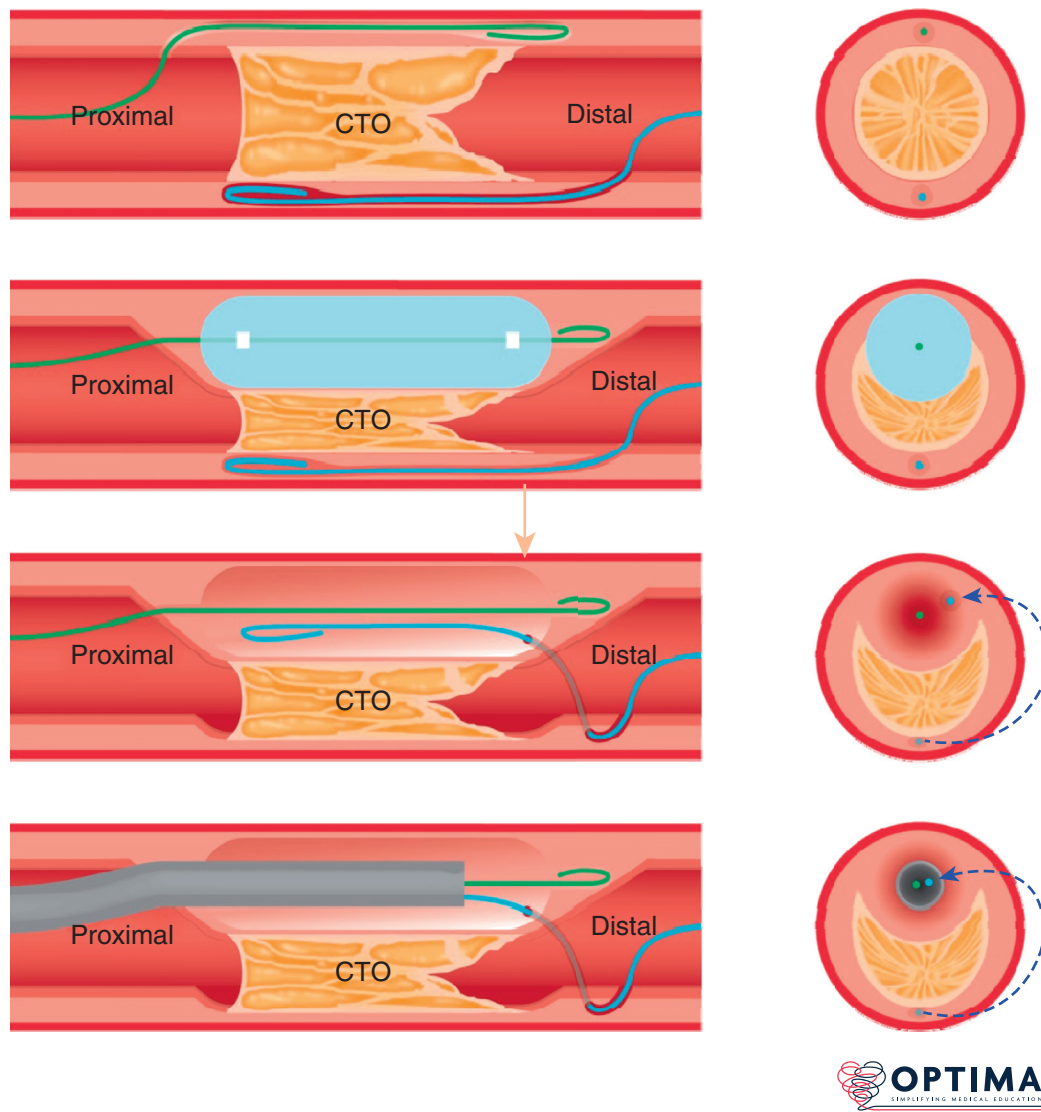


FIGURE 9.9 Reverse controlled antegrade and retrograde subintimal tracking (CART) method. The reverse CART method is the most commonly used technique for retrograde dissection reentry. An angioplasty balloon catheter is advanced over the antegrade wire and then advanced to the reentry zone. The balloon is inflated to create a larger subintimal space, and the retrograde wire is then used to advance into this space, thereby establishing a connection between the antegrade and retrograde spaces. The retrograde microcatheter is then advanced into the antegrade guide catheter, and the procedure is completed in an antegrade fashion over the externalized wire. CTO, Chronic total occlusion. (Courtesy of Dr. James Spratt, Optima Education.)

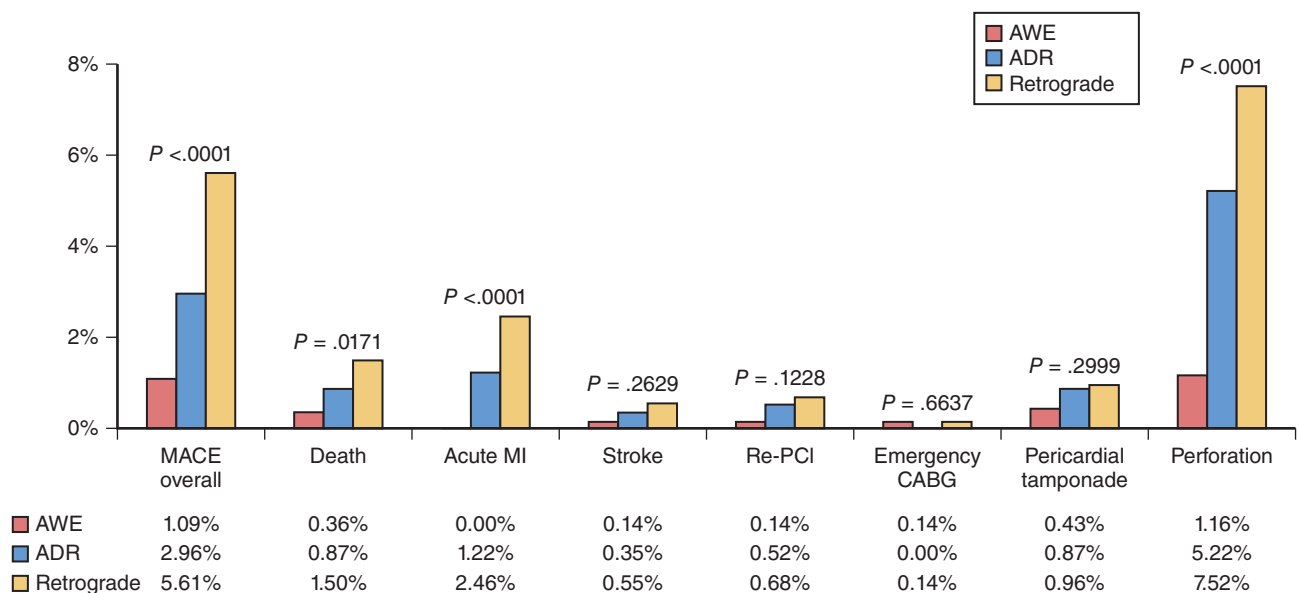


FIGURE 9.10 Major complication rates according to final successful chronic total occlusion (CTO) crossing strategy in the Prospective Global Registry for the Study of Chronic Total Occlusion Intervention (PROGRESS-CTO) registry. ADR, Antegrade dissection and reentry; AWE, antegrade wire escalation; CABG, coronary artery bypass grafting; MACE, major adverse cardiovascular event. (Reproduced from Tajti P, Karpaliotis D, Alaswad K, et al. The hybrid approach to chronic total occlusion percutaneous coronary intervention: update from the PROGRESS CTO registry. *JACC Cardiovasc Interv.* 2018;11:1325-1335.)

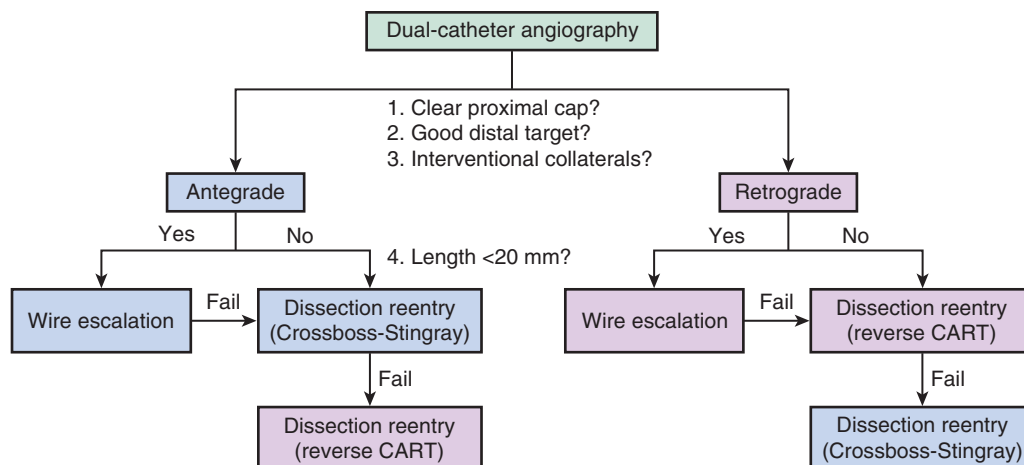


FIGURE 9.11 Hybrid strategy for chronic total occlusion (CTO) percutaneous coronary intervention. The hybrid strategy incorporates antegrade, retrograde, and dissection and reentry techniques into an algorithm based on angiographic characteristics of the CTO. CART, Controlled antegrade and retrograde subintimal tracking.

identifying best angiographic projection and providing a directional guide through the occluded segment not visualized by conventional fluoroscopy.¹¹¹

Intravascular ultrasonography has an important role in both the evaluation and treatment of CTOs. IVUS can be useful in identifying proximal cap location; confirming wire penetration into the proximal cap; redirecting the wire into the true lumen after penetrating the subintimal space; and optimizing stent placement, expansion, and apposition.¹¹²

COMPLICATIONS OF CTO PCI

Angioplasty of a CTO has traditionally been considered benign, with the presupposition that because the artery is already occluded with collateral circulation, no harm can be done. However, the increased technical complexity of CTO PCI is associated with a twofold higher risk of periprocedural complications than non-CTO PCI.¹⁰ Contemporary data from the PROGRESS CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) (see Figure 9.10), OPEN-CTO (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Registry), and RECHARGE (Registry of Crossboss and Hybrid procedures in France, the Netherlands, Belgium and United Kingdom) registries showed a major complication rate around 3% to 4% at experienced centers.^{31,94,95} Coronary perforation is the most feared complication and among experienced CTO operators. Coronary perforation requiring treatment occurred in 4.8% of patients in one registry.³¹ Management of perforations includes (1) prolonged inflation across the perforation with an occluding balloon (2) reversal of anticoagulation (after removal of intracoronary devices), (3) covered stent placement, (4) emergency surgery, (5) embolization, and (6) pericardiocentesis. To avoid target or donor vessel thrombosis, reversal of anticoagulation is generally not recommended in coronary perforations provided that hemostasis can be achieved by mechanical means before gear removal. Other procedure-related complications include thrombus formation, coronary dissection, and side branch or collateral occlusion,

leading to periprocedural MI. Catheter entrapment is also an uncommon but reported complication. Although not specific to CTO PCI, contrast nephropathy and radiation injury can also occur. Contrast-induced nephropathy is a complication that is dose dependent to contrast exposure with increasing risk relative to baseline renal impairment. Similarly, radiation-induced dermal injury is dose dependent and requires careful surveillance in patients who receive significant radiation exposure. Fluoroscopic time is inadequate for measuring radiation exposure, but instead total air kerma at the interventional reference point (x-ray energy delivered to air) should be used to monitor deterministic skin effects. Measures to reduce focal radiation exposure include collimation, frequent changing of viewing projections, and reduction in fluoroscopic frame rates. A radiation dose greater than 5 Gy air kerma should prompt operators to consider aborting the CTO-PCI attempt if substantial progress or lesion crossing has not occurred.²³

CONCLUSIONS

The implications of improving early procedural and long-term clinical outcomes among patients with CTOs are considerable. Until recently, however, our knowledge of procedural, angiographic, and clinical outcomes after PCI for CTOs was limited by the systematic or preferential exclusion of patients with CTO target lesions from major interventional cardiology clinical trials. Furthermore, no technology is presently available to reliably predict or facilitate procedural success in patients considered for CTO revascularization. In comparison with revascularization for nonocclusive lesions, the complexity of CTOs is reflected in differences regarding lesion length, plaque burden, negative vascular remodeling, thrombus, and calcification.

Although the challenges associated with CTOs may seem formidable, it is equally clear that our evolving understanding of the benefits of revascularization has contributed to increasing interest in CTOs, reflected in an

increasing number of CTO procedures, the development of novel technologies, and the design of trials dedicated to CTO revascularization. Over the past decade, a number of alternative technologies and techniques have been advanced, including sophisticated antegrade and retrograde guidewire methods, microdissection, and device-assisted luminal reentry. Noninvasive imaging has further enhanced patient candidacy for CTO PCI through assessment of myocardial viability and clarification of ambiguous coronary anatomy. Despite greater resource use, CTO PCI is not an economic disincentive.¹¹³ Altogether, the learning curve for advanced CTO techniques has never been more abbreviated through expansion of clinical trials, regional and international educational sessions, online didactic programs, direct proctoring, and more recently dedicated fellowship training programs.

Thus, although CTOs reflect the current inadequacies in PCI methods to achieving initial procedural success and for sustaining restenosis-free patency after initial success, they also represent a unique opportunity to conquer perhaps the most difficult and yet one of the most common lesion subsets in interventional cardiology. Although there remains opportunity for improvement, the advancement of innovative techniques and technologies that may safely improve outcome in a lesion complexity, termed the “last great barrier to PCI success,” is welcomed.

Visit Elsevier eBooks+ to access the complete list of references.

SELECTED REFERENCES

2. Fefer P, Knudtson ML, Cheema AN, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol*. 2012;59:991-997.
9. Grantham JA, Marso SP, Spertus J, House J, Holmes DR Jr, Rutherford BD. Chronic total occlusion angioplasty in the United States. *JACC Cardiovasc Interv*. 2009;2:479-486.
10. Brilakis ES, Banerjee S, Karpaliotis D, et al. Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv*. 2015;8:245-253.
11. Farooq V, Serruys PW, Garcia-Garcia HM, et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol*. 2013;61:282-294.
12. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:2574-2609.
13. Stone GW, Kandzari DE, Mehran R, et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. *Circulation*. 2005;112:2364-2372.
20. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. [2018 ESC/EACTS guidelines on myocardial revascularization]. *Kardiol Pol*. 2018;76:1585-1664.
21. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: A Report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation*. 2009;119:1330-1352.
22. Patel MR, Calhoun JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 Appropriate Use Criteria for Coronary Revascularization in Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;69:570-591.
23. Brilakis ES, Mashayekhi K, Tsuchikane E, et al. Guiding principles for chronic total occlusion percutaneous coronary intervention. *Circulation*. 2019;140:420-433.
29. Schumacher SP, Stuijzand WJ, de Winter RW, et al. Ischemic burden reduction and long-term clinical outcomes after chronic total occlusion percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2021;14:1407-1418.
30. Obedinskiy AA, Kretov EI, Boukhris M, et al. The IMPACTOR-CTO Trial. *JACC Cardiovasc Interv*. 2018;11:1309-1311.
31. Saponitis J, Salisbury AC, Yeh RW, et al. Early procedural and health status outcomes after chronic total occlusion angioplasty: a report from the OPEN-CTO Registry (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures). *JACC Cardiovasc Interv*. 2017;10:1523-1534.
32. Werner GS, Martin-Yuste V, Hildick-Smith D, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J*. 2018;39:2484-2493.
35. Kandzari DE, Lembo NJ, Carlson HD, et al. Procedural, clinical, and health status outcomes in chronic total coronary occlusion revascularization: results from the PERSPECTIVE study. *Catheter Cardiovasc Interv*. 2020;96:567-576.
36. Hirai T, Grantham JA, Saponitis J, et al. Quality of life changes after chronic total occlusion angioplasty in patients with baseline refractory angina. *Circ Cardiovasc Interv*. 2019;12:e007558.
39. Megaly M, Saad M, Tajti P, et al. Meta-analysis of the impact of successful chronic total occlusion percutaneous coronary intervention on left ventricular systolic function and reverse remodeling. *J Interv Cardiol*. 2018;31:562-571.
42. Baks T, van Geuns RJ, Duncker DJ, et al. Prediction of left ventricular function after drug-eluting stent implantation for chronic total coronary occlusions. *J Am Coll Cardiol*. 2006;47:721-725.
43. Werner GS, Surber R, Kuethe F, et al. Collaterals and the recovery of left ventricular function after recanalization of a chronic total coronary occlusion. *Am Heart J*. 2005;149:129-137.
44. Henriques JP, Hoesbers LP, Ramunddal T, et al. Percutaneous intervention for concurrent chronic total occlusions in patients With STEMI: the EXPLORE trial. *J Am Coll Cardiol*. 2016;68:1622-1632.
46. Mashayekhi K, Nuhrenberg TG, Toma A, et al. A randomized trial to assess regional left ventricular function after stent implantation in chronic total occlusion: the REVASC trial. *JACC Cardiovasc Interv*. 2018;11:1982-1991.
49. Nombela-Franco L, Mitroi CD, Fernandez-Lozano I, et al. Ventricular arrhythmias among implantable cardioverter-defibrillator recipients for primary prevention: impact of chronic total coronary occlusion (VACTO Primary Study). *Circ Arrhythm Electrophysiol*. 2012;5:147-154.
52. Claessen BE, Dangas GD, Weisz G, et al. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *Eur Heart J*. 2012;33:768-775.
54. Lexis CP, van der Horst IC, Rahel BM, et al. Impact of chronic total occlusions on markers of reperfusion, infarct size, and long-term mortality: a substudy from the TAPAS-trial. *Catheter Cardiovasc Interv*. 2011;77:484-491.
59. Jang WJ, Yang JH, Choi SH, et al. Long-term survival benefit of revascularization compared with medical therapy in patients with coronary chronic total occlusion and well-developed collateral circulation. *JACC Cardiovasc Interv*. 2015;8:271-279.
60. Lee SW, Lee PH, Ahn JM, et al. Randomized trial evaluating percutaneous coronary intervention for the treatment of chronic total occlusion. *Circulation*. 2019;139:1674-1683.
63. Jones DA, Weerackody R, Rathod K, et al. Successful recanalization of chronic total occlusions is associated with improved long-term survival. *JACC Cardiovasc Interv*. 2012;5:380-388.
66. Genereux P, Palmerini T, Caixeta A, et al. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. *J Am Coll Cardiol*. 2012;59:2165-2174.
67. Ybarra LF, Rinfret S, Brilakis ES, et al. Definitions and clinical trial design principles for coronary artery chronic total occlusion therapies: CTO-ARC consensus recommendations. *Circulation*. 2021;143:479-500.
73. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol*. 1985;5:587-592.
76. Werner GS, Ferrari M, Heinke S, et al. Angiographic assessment of collateral connections in comparison with invasively determined collateral function in chronic coronary occlusions. *Circulation*. 2003;107:1972-1977.
80. Safley DM, House JA, Marso SP, Grantham JA, Rutherford BD. Improvement in survival following successful percutaneous coronary intervention of coronary chronic total occlusions: variability by target vessel. *JACC Cardiovasc Interv*. 2008;1:295-302.
81. Morino Y, Abe M, Morimoto T, et al. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. *JACC Cardiovasc Interv*. 2011;4:213-221.
82. Christopoulos G, Kandzari DE, Yeh RW, et al. Development and validation of a novel scoring system for predicting technical success of chronic total occlusion percutaneous coronary interventions: the PROGRESS CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) Score. *JACC Cardiovasc Interv*. 2016;9:1-9.



83. Maeremans J, Spratt JC, Knaapen P, et al. Towards a contemporary, comprehensive scoring system for determining technical outcomes of hybrid percutaneous chronic total occlusion treatment: the RECHARGE score. *Catheter Cardiovasc Interv*. 2018;91:192-202.
84. Christopoulos G, Wyman RM, Alaswad K, et al. Clinical utility of the Japan-chronic total occlusion score in coronary chronic total occlusion interventions: results from a multicenter registry. *Circ Cardiovasc Interv*. 2015;8:e002171.
85. Kinnaird T, Anderson R, Ossei-Gerning N, et al. Vascular access site and outcomes among 26,807 chronic total coronary occlusion angioplasty cases from the British Cardiovascular Interventions Society National Database. *JACC Cardiovasc Interv*. 2017;10:635-644.
86. Megaly M, Karatasakis A, Abraham B, et al. Radial versus femoral access in chronic total occlusion percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2019;12:e007778.
90. Kandzari DE, Alaswad K, Jaffer FA, et al. Safety and efficacy of dedicated guidewire, microcatheter, and guide catheter extension technologies for chronic total coronary occlusion revascularization: primary results of the Teleflex Chronic Total Occlusion Study. *Catheter Cardiovasc Interv*. 2022;99(2):263-270.
91. Kandzari DE, Grantham JA, Karpaliotis D, et al. Safety and efficacy of dedicated guidewire and microcatheter technology for chronic total coronary occlusion revascularization: principal results of the Asahi Intecc Chronic Total Occlusion Study. *Coron Artery Dis*. 2018;29:618-623.
93. Brilakis ES, Grantham JA, Rinfret S, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. *JACC Cardiovasc Interv*. 2012;5:367-379.
94. Tajti P, Karpaliotis D, Alaswad K, et al. The hybrid approach to chronic total occlusion percutaneous coronary intervention: update from the PROGRESS CTO Registry. *JACC Cardiovasc Interv*. 2018;11:1325-1335.
95. Maeremans J, Walsh S, Knaapen P, et al. The hybrid algorithm for treating chronic total occlusions in europe: the RECHARGE Registry. *J Am Coll Cardiol*. 2016;68:1958-1970.
96. Colombo A, Mikhail GW, Michev I, et al. Treating chronic total occlusions using subintimal tracking and reentry: the STAR technique. *Catheter Cardiovasc Interv*. 2005;64:407-411; discussion 412.
98. Goleski PJ, Nakamura K, Liebeskind E, et al. Revascularization of coronary chronic total occlusions with subintimal tracking and reentry followed by deferred stenting: experience from a high-volume referral center. *Catheter Cardiovasc Interv*. 2019;93:191-198.
100. Karacsonyi J, Tajti P, Rangan BV, et al. Randomized comparison of a CrossBoss first versus standard wire escalation strategy for crossing coronary chronic total occlusions: the CrossBoss First trial. *JACC Cardiovasc Interv*. 2018;11:225-233.
101. Maeremans J, Dens J, Spratt JC, et al. Antegrade dissection and reentry as part of the hybrid chronic total occlusion revascularization strategy: a subanalysis of the RECHARGE Registry (Registry of CrossBoss and Hybrid Procedures in France, the Netherlands, Belgium and United Kingdom). *Circ Cardiovasc Interv*. 2017;10(6):e004791.
105. Surmely JF, Tsuchikane E, Katoh O, et al. New concept for CTO recanalization using controlled antegrade and retrograde subintimal tracking: the CART technique. *J Invasive Cardiol*. 2006;18:334-338.
108. Joyal D, Thompson CA, Grantham JA, Buller CE, Rinfret S. The retrograde technique for recanalization of chronic total occlusions: a step-by-step approach. *JACC Cardiovasc Interv*. 2012;5:1-11.
109. Megaly M, Ali A, Saad M, et al. Outcomes with retrograde versus antegrade chronic total occlusion revascularization. *Catheter Cardiovasc Interv*. 2020;96:1037-1043.

REFERENCES

- Serruys PW, Ono M, Garg S, et al. Percutaneous coronary revascularization: JACC historical breakthroughs in perspective. *J Am Coll Cardiol*. 2021;78:384-407.
- Fefer P, Knudtson ML, Cheema AN, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol*. 2012;59:991-997.
- Jeroudi OM, Alomar ME, Michael TT, et al. Prevalence and management of coronary chronic total occlusions in a tertiary Veterans Affairs hospital. *Catheter Cardiovasc Interv*. 2014;84:637-643.
- Rupprecht HJ, Hamm C, Ischinger T, Dietz U, Reimers J, Meyer J. Angiographic follow-up results of a randomized study on angioplasty versus bypass surgery (GABI trial). *Eur Heart J*. 1996;17:1192-1198.
- Pereg D, Fefer P, Samuel M, et al. Native coronary artery patency after coronary artery bypass surgery. *JACC Cardiovasc Interv*. 2014;7:761-767.
- Dautov R, Manh Nguyen C, Altisent O, Gibrat C, Rinfret S. Recanalization of chronic total occlusions in patients with previous coronary bypass surgery and consideration of retrograde access via saphenous vein grafts. *Circ Cardiovasc Interv*. 2016;9(7):e003515.
- Christofferson RD, Lehmann KG, Martin GV, Every N, Caldwell JH, Kapadia SR. Effect of chronic total coronary occlusion on treatment strategy. *Am J Cardiol*. 2005;95:1088-1091.
- Abbott JD, Kip KE, Vlachos HA, et al. Recent trends in the percutaneous treatment of chronic total coronary occlusions. *Am J Cardiol*. 2006;97:1691-1696.
- Grantham JA, Marso SP, Spertus J, House J, Holmes DR Jr, Rutherford BD. Chronic total occlusion angioplasty in the United States. *JACC Cardiovasc Interv*. 2009;2:479-486.
- Brilakis ES, Banerjee S, Karpaliotis D, et al. Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv*. 2015;8:245-253.
- Farooq V, Serruys PW, Garcia-Garcia HM, et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol*. 2013;61:282-294.
- Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:2574-2609.
- Stone GW, Kandzari DE, Mehran R, et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. *Circulation*. 2005;112:2364-2372.
- Tomasello SD, Boukhris M, Giubilato S, et al. Management strategies in patients affected by chronic total occlusions: results from the Italian Registry of Chronic Total Occlusions. *Eur Heart J*. 2015;36:3189-3198.
- Olivari Z, Rubartelli P, Piscione F, et al. Immediate results and one-year clinical outcome after percutaneous coronary interventions in chronic total occlusions: data from a multicenter, prospective, observational study (TOAST-GISE). *J Am Coll Cardiol*. 2003;41:1672-1678.
- He ZX, Mahmarian JJ, Verani MS. Myocardial perfusion in patients with total occlusion of a single coronary artery with and without collateral circulation. *J Nucl Cardiol*. 2001;8:452-457.
- Aboul-Enein F, Kar S, Hayes SW, et al. Influence of angiographic collateral circulation on myocardial perfusion in patients with chronic total occlusion of a single coronary artery and no prior myocardial infarction. *J Nucl Med*. 2004;45:950-955.
- Stuijzand WJ, Driessen RS, Raijmakers PG, et al. Prevalence of ischaemia in patients with a chronic total occlusion and preserved left ventricular ejection fraction. *Eur Heart J Cardiovasc Imaging*. 2017;18:1025-1033.
- Stone GW, Reifart NJ, Moussa I, et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part II. *Circulation*. 2005;112:2530-2537.
- Neumann FJ, Sousa-Uva M, Ahlsson A, et al. [2018 ESC/EACTS guidelines on myocardial revascularization]. *Kardiol Pol*. 2018;76:1585-1664.
- Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation*. 2009;119:1330-1352.
- Patel MR, Calhoun JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 appropriate use criteria for coronary revascularization in patients with acute coronary syndromes: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;69:570-591.
- Brilakis ES, Mashayekhi K, Tsuchikane E, et al. Guiding principles for chronic total occlusion percutaneous coronary intervention. *Circulation*. 2019;140:420-433.
- Rinfret S, Sandesara PB. Reducing ischemia with CTO PCI: good news, but questions remain. *JACC Cardiovasc Interv*. 2021;14:1419-1422.
- Sachdeva R, Agrawal M, Flynn SE, Werner GS, Uretsky BF. The myocardium supplied by a chronic total occlusion is a persistently ischemic zone. *Catheter Cardiovasc Interv*. 2014;83:9-16.
- Galassi AR, Werner GS, Tomasello SD, et al. Prognostic value of exercise myocardial scintigraphy in patients with coronary chronic total occlusions. *J Interv Cardiol*. 2010;23:139-148.
- Safley DM, Koshy S, Grantham JA, et al. Changes in myocardial ischemic burden following percutaneous coronary intervention of chronic total occlusions. *Catheter Cardiovasc Interv*. 2011;78:337-343.
- Stuijzand WJ, Biesbroek PS, Raijmakers PG, et al. Effects of successful percutaneous coronary intervention of chronic total occlusions on myocardial perfusion and left ventricular function. *EuroIntervention*. 2017;13:345-354.
- Schumacher SP, Stuijzand WJ, de Winter RW, et al. Ischemic burden reduction and long-term clinical outcomes after chronic total occlusion percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2021;14:1407-1418.
- Obedinskiy AA, Kretov EI, Boukhris M, et al. The IMPACTOR-CTO Trial. *JACC Cardiovasc Interv*. 2018;11:1309-1311.
- Sapontis J, Salisbury AC, Yeh RW, et al. Early procedural and health status outcomes after chronic total occlusion angioplasty: a report from the OPEN-CTO Registry (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures). *JACC Cardiovasc Interv*. 2017;10:1523-1534.
- Werner GS, Martin-Yuste V, Hildick-Smith D, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J*. 2018;39:2484-2493.
- Christakopoulos GE, Christopoulos G, Carlino M, et al. Meta-analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. *Am J Cardiol*. 2015;115:1367-1375.
- Joyal D, Afilalo J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. *Am Heart J*. 2010;160:179-187.
- Kandzari DE, Lembo NJ, Carlson HD, et al. Procedural, clinical, and health status outcomes in chronic total coronary occlusion revascularization: results from the PERSPECTIVE study. *Catheter Cardiovasc Interv*. 2020;96:567-576.
- Hirai T, Grantham JA, Sapontis J, et al. Quality of life changes after chronic total occlusion angioplasty in patients with baseline refractory angina. *Circ Cardiovasc Interv*. 2019;12:e007558.
- Panza JA, Chrzanowski L, Bonow RO. Myocardial viability assessment before surgical revascularization in ischemic cardiomyopathy: JACC review topic of the week. *J Am Coll Cardiol*. 2021;78:1068-1077.
- Galassi AR, Boukhris M, Toma A, et al. Percutaneous coronary intervention of chronic total occlusions in patients with low left ventricular ejection fraction. *JACC Cardiovasc Interv*. 2017;10:2158-2170.
- Megaly M, Saad M, Tajti P, et al. Meta-analysis of the impact of successful chronic total occlusion percutaneous coronary intervention on left ventricular systolic function and reverse remodeling. *J Interv Cardiol*. 2018;31:562-571.
- Hoebbers LP, Claessen BE, Elias J, Dangas GD, Mehran R, Henriques JP. Meta-analysis on the impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcome. *Int J Cardiol*. 2015;187:90-96.
- Cheng AS, Selvanayagam JB, Jerosch-Herold M, et al. Percutaneous treatment of chronic total coronary occlusions improves regional hyperemic myocardial blood flow and contractility: insights from quantitative cardiovascular magnetic resonance imaging. *JACC Cardiovasc Interv*. 2008;1:44-53.
- Baks T, van Geuns RJ, Duncker DJ, et al. Prediction of left ventricular function after drug-eluting stent implantation for chronic total coronary occlusions. *J Am Coll Cardiol*. 2006;47:721-725.
- Werner GS, Surber R, Kuethe F, et al. Collaterals and the recovery of left ventricular function after recanalization of a chronic total coronary occlusion. *Am Heart J*. 2005;149:129-137.
- Henriques JP, Hoebbers LP, Ramunddal T, et al. Percutaneous intervention for concurrent chronic total occlusions in patients with STEMI: the EXPLORE trial. *J Am Coll Cardiol*. 2016;68:1622-1632.
- Elias J, van Dongen IM, Hoebbers LP, et al. Improved recovery of regional left ventricular function after PCI of chronic total occlusion in STEMI patients: a cardiovascular magnetic resonance study of the randomized controlled EXPLORE trial. *J Cardiovasc Magn Reson*. 2017;19:53.
- Mashayekhi K, Nuhrenberg TG, Toma A, et al. A randomized trial to assess regional left ventricular function after stent implantation in chronic total occlusion: the REVASC trial. *JACC Cardiovasc Interv*. 2018;11:1982-1991.
- Kirschbaum SW, Baks T, van den Ent M, et al. Evaluation of left ventricular function three years after percutaneous recanalization of chronic total coronary occlusions. *Am J Cardiol*. 2008;101:179-185.
- Di Carli MF, Asgarzade F, Schelbert HR, et al. Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy. *Circulation*. 1995;92:3436-3444.
- Nombela-Franco L, Mitroi CD, Fernandez-Lozano I, et al. Ventricular arrhythmias among implantable cardioverter-defibrillator recipients for primary prevention: impact of chronic total coronary occlusion (VACTO Primary Study). *Circ Arrhythm Electrophysiol*. 2012;5:147-154.
- Nombela-Franco L, Iannaccone M, Anguera I, et al. Impact of Chronic Total Coronary Occlusion on Recurrence of Ventricular Arrhythmias in Ischemic



- Secondary Prevention Implantable Cardioverter-Defibrillator Recipients (VACTO Secondary Study): insights from coronary angiogram and electrogram analysis. *JACC Cardiovasc Interv.* 2017;10:879-888.
51. Watanabe H, Morimoto T, Shiomi H, et al. Chronic total occlusion in non-infarct-related artery is associated with increased short-and long-term mortality in patients with ST-segment elevation acute myocardial infarction complicated by cardiogenic shock (from the CREDO-Kyoto AMI registry). *Catheter Cardiovasc Interv.* 2018;92:455-463.
52. Claessen BE, Dangas GD, Weisz G, et al. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *Eur Heart J.* 2012;33:768-775.
53. Claessen BE, van der Schaaf RJ, Verouden NJ, et al. Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. *JACC Cardiovasc Interv.* 2009;2:1128-1134.
54. Lexis CP, van der Horst IC, Rahel BM, et al. Impact of chronic total occlusions on markers of reperfusion, infarct size, and long-term mortality: a substudy from the TAPAS-trial. *Catheter Cardiovasc Interv.* 2011;77:484-491.
55. O'Connor SA, Garot P, Sanguineti F, et al. Meta-analysis of the impact on mortality of noninfarct-related artery coronary chronic total occlusion in patients presenting with ST-segment elevation myocardial infarction. *Am J Cardiol.* 2015;116:8-14.
56. Smits PC, Boxma-de Klerk BM. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med.* 2017;377:397-398.
57. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med.* 2013;369:1115-1123.
58. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol.* 2015;65:963-972.
59. Jang WJ, Yang JH, Choi SH, et al. Long-term survival benefit of revascularization compared with medical therapy in patients with coronary chronic total occlusion and well-developed collateral circulation. *JACC Cardiovasc Interv.* 2015;8:271-279.
60. Lee SW, Lee PH, Ahn JM, et al. Randomized trial evaluating percutaneous coronary intervention for the treatment of chronic total occlusion. *Circulation.* 2019;139:1674-1683.
61. Brilakis ES, Mashayekhi K, Burke MN. How DECISION-CTO can help guide the decision to perform chronic total occlusion percutaneous coronary intervention. *Circulation.* 2019;139:1684-1687.
62. Suero JA, Marso SP, Jones PG, et al. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: a 20-year experience. *J Am Coll Cardiol.* 2001;38:409-414.
63. Jones DA, Weerackody R, Rathod K, et al. Successful recanalization of chronic total occlusions is associated with improved long-term survival. *JACC Cardiovasc Interv.* 2012;5:380-388.
64. Hannan EL, Wu C, Walford G, et al. Incomplete revascularization in the era of drug-eluting stents: impact on adverse outcomes. *JACC Cardiovasc Interv.* 2009;2:17-25.
65. Iqbal MB, Moore PT, Nadra IJ, et al. Complete revascularization in stable multivessel coronary artery disease: a real world analysis from the British Columbia Cardiac Registry. *Catheter Cardiovasc Interv.* 2022;99(3):627-638.
66. Genereux P, Palmerini T, Caixeta A, et al. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. *J Am Coll Cardiol.* 2012;59:2165-2174.
67. Ybarra LF, Rinfret S, Brilakis ES, et al. Definitions and clinical trial design principles for coronary artery chronic total occlusion therapies: CTO-ARC Consensus Recommendations. *Circulation.* 2021;143:479-500.
68. Srivatsa SS, Edwards WD, Boos CM, et al. Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. *J Am Coll Cardiol.* 1997;29:955-963.
69. Sakakura K, Nakano M, Otsuka F, et al. Comparison of pathology of chronic total occlusion with and without coronary artery bypass graft. *Eur Heart J.* 2014;35:1683-1693.
70. Katsuragawa M, Fujiwara H, Miyamae M, Sasayama S. Histologic studies in percutaneous transluminal coronary angioplasty for chronic total occlusion: comparison of tapering and abrupt types of occlusion and short and long occluded segments. *J Am Coll Cardiol.* 1993;21:604-611.
71. Galassi AR, Tomasello SD, Crea F, et al. Transient impairment of vasomotion function after successful chronic total occlusion recanalization. *J Am Coll Cardiol.* 2012;59:711-718.
72. Kumamoto M, Nakashima Y, Sueishi K. Intimal neovascularization in human coronary atherosclerosis: its origin and pathophysiological significance. *Hum Pathol.* 1995;26:450-456.
73. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol.* 1985;5:587-592.
74. Surmely JF, Katoh O, Tsuchikane E, Nasu K, Suzuki T. Coronary septal collaterals as an access for the retrograde approach in the percutaneous treatment of coronary chronic total occlusions. *Catheter Cardiovasc Interv.* 2007;69:826-832.
75. Werner GS. The role of coronary collaterals in chronic total occlusions. *Curr Cardiol Rev.* 2014;10:57-64.
76. Werner GS, Ferrari M, Heinke S, et al. Angiographic assessment of collateral connections in comparison with invasively determined collateral function in chronic coronary occlusions. *Circulation.* 2003;107:1972-1977.
77. McEntegart MB, Badar AA, Ahmad FA, et al. The collateral circulation of coronary chronic total occlusions. *EuroIntervention.* 2016;11:e1596-e1603.
78. Werner GS, Figulla HR. Direct assessment of coronary steal and associated changes of collateral hemodynamics in chronic total coronary occlusions. *Circulation.* 2002;106:435-440.
79. Puma JA, Sketch MH Jr, Thompson TD, et al. Support for the open-artery hypothesis in survivors of acute myocardial infarction: analysis of 11,228 patients treated with thrombolytic therapy. *Am J Cardiol.* 1999;83:482-487.
80. Safley DM, House JA, Marso SP, Grantham JA, Rutherford BD. Improvement in survival following successful percutaneous coronary intervention of coronary chronic total occlusions: variability by target vessel. *JACC Cardiovasc Interv.* 2008;1:295-302.
81. Morino Y, Abe M, Morimoto T, et al. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. *JACC Cardiovasc Interv.* 2011;4:213-221.
82. Christopoulos G, Kandzari DE, Yeh RW, et al. Development and validation of a novel scoring system for predicting technical success of chronic total occlusion percutaneous coronary interventions: the PROGRESS CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) Score. *JACC Cardiovasc Interv.* 2016;9:1-9.
83. Maeremans J, Spratt JC, Knaapen P, et al. Towards a contemporary, comprehensive scoring system for determining technical outcomes of hybrid percutaneous chronic total occlusion treatment: the RECHARGE score. *Catheter Cardiovasc Interv.* 2018;91:192-202.
84. Christopoulos G, Wyman RM, Alaswad K, et al. Clinical utility of the Japan-chronic total occlusion score in coronary chronic total occlusion interventions: results from a multicenter registry. *Circ Cardiovasc Interv.* 2015;8:e002171.
85. Kinnaird T, Anderson R, Ossei-Gerning N, et al. Vascular access site and outcomes among 26,807 chronic total coronary occlusion angioplasty cases from the British Cardiovascular Interventions Society National Database. *JACC Cardiovasc Interv.* 2017;10:635-644.
86. Megaly M, Karatasakis A, Abraham B, et al. Radial versus femoral access in chronic total occlusion percutaneous coronary intervention. *Circ Cardiovasc Interv.* 2019;12:e007778.
87. Dautov R, Ribeiro HB, Abdul-Jawad Altisent O, et al. Effectiveness and safety of the transradial 8fr sheathless approach for revascularization of chronic total occlusions. *Am J Cardiol.* 2016;118:785-789.
88. Spratt JC, Hanratty C, Walsh S, Wilson S. *A Guide to Mastering Antegrade CTO PCI Part 1.* Optima Education; 2019.
89. Kini AS, Rafael OC, Sarkar K, et al. Changing outcomes and treatment strategies for wire induced coronary perforations in the era of bivalirudin use. *Catheter Cardiovasc Interv.* 2009;74:700-707.
90. Kandzari DE, Alaswad K, Jaffer FA, et al. Safety and efficacy of dedicated guidewire, microcatheter, and guide catheter extension technologies for chronic total coronary occlusion revascularization: primary results of the Teleflex Chronic Total Occlusion Study. *Catheter Cardiovasc Interv.* 2022;99(2):263-270.
91. Kandzari DE, Grantham JA, Karpaliotis D, et al. Safety and efficacy of dedicated guidewire and microcatheter technology for chronic total coronary occlusion revascularization: principal results of the Asahi Intec Chronic Total Occlusion Study. *Coron Artery Dis.* 2018;29:618-623.
92. McNeice A, Ladwiniec A, Walsh S, Hanratty C. Hybrid approach to percutaneous coronary intervention to treat chronic total occlusions. *Eur Cardiol.* 2017;12:46-51.
93. Brilakis ES, Grantham JA, Rinfret S, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. *JACC Cardiovasc Interv.* 2012;5:367-379.
94. Tajti P, Karpaliotis D, Alaswad K, et al. The hybrid approach to chronic total occlusion percutaneous coronary intervention: update from the PROGRESS CTO Registry. *JACC Cardiovasc Interv.* 2018;11:1325-1335.
95. Maeremans J, Walsh S, Knaapen P, et al. The hybrid algorithm for treating chronic total occlusions in Europe: the RECHARGE Registry. *J Am Coll Cardiol.* 2016;68:1958-1970.
96. Colombo A, Mikhail GW, Michev I, et al. Treating chronic total occlusions using subintimal tracking and reentry: the STAR technique. *Catheter Cardiovasc Interv.* 2005;64:407-411; discussion 412.
97. Hirai T, Grantham JA, Sapontis J, et al. Impact of subintimal plaque modification procedures on health status after unsuccessful chronic total occlusion angioplasty. *Catheter Cardiovasc Interv.* 2018;91:1035-1042.
98. Galeski PJ, Nakamura K, Liebeskind E, et al. Revascularization of coronary chronic total occlusions with subintimal tracking and reentry followed by deferred stenting: experience from a high-volume referral center. *Catheter Cardiovasc Interv.* 2019;93:191-198.
99. Davies RE, Rier JD, McEntegart M, Riley RF, Kearney K, Lombardi W. Subintimal tracking and reentry as a tool in CTO-PCI: past, present, and future. *Catheter Cardiovasc Interv.* 2021;98(6):1144-1151.
100. Karacsonyi J, Tajti P, Rangan BV, et al. Randomized comparison of a cross-boss first versus standard wire escalation strategy for crossing coronary chronic total occlusions: the CrossBoss First trial. *JACC Cardiovasc Interv.* 2018;11:225-233.
101. Maeremans J, Dens J, Spratt JC, et al. Antegrade dissection and reentry as part of the hybrid chronic total occlusion revascularization strategy: a

- subanalysis of the RECHARGE Registry (Registry of CrossBoss and Hybrid Procedures in France, the Netherlands, Belgium and United Kingdom). *Circ Cardiovasc Interv.* 2017;10(6):e004791.
102. Azzalini L, Dautov R, Brilakis ES, et al. Procedural and longer-term outcomes of wire- versus device-based antegrade dissection and re-entry techniques for the percutaneous revascularization of coronary chronic total occlusions. *Int J Cardiol.* 2017;231:78-83.
 103. Walsh SJ, Hanratty CG, McEntegart M, et al. Intravascular healing is not affected by approaches in contemporary CTO PCI: the CONSISTENT CTO study. *JACC Cardiovasc Interv.* 2020;13:1448-1457.
 104. Megaly M, Xenogiannis I, Abi Rafeh N, et al. Retrograde approach to chronic total occlusion percutaneous coronary intervention. *Circ Cardiovasc Interv.* 2020;13:e008900.
 105. Surmely JF, Tsuchikane E, Katoh O, et al. New concept for CTO recanalization using controlled antegrade and retrograde subintimal tracking: the CART technique. *J Invasive Cardiol.* 2006;18:334-338.
 106. Karpaliotis D, Karatasakis A, Alaswad K, et al. Outcomes with the use of the retrograde approach for coronary chronic total occlusion interventions in a contemporary multicenter US registry. *Circ Cardiovasc Interv.* 2016;9(6). doi:10.1161/CIRCINTERVENTIONS.115.003434.
 107. Konstantinidis NV, Werner GS, Deffereos S, et al. Temporal trends in chronic total occlusion interventions in Europe. *Circ Cardiovasc Interv.* 2018;11:e006229.
 108. Joyal D, Thompson CA, Grantham JA, Buller CE, Rinfret S. The retrograde technique for recanalization of chronic total occlusions: a step-by-step approach. *JACC Cardiovasc Interv.* 2012;5:1-11.
 109. Megaly M, Ali A, Saad M, et al. Outcomes with retrograde versus antegrade chronic total occlusion revascularization. *Catheter Cardiovasc Interv.* 2020;96:1037-1043.
 110. Mollet NR, Hoyer A, Lemos PA, et al. Value of preprocedure multislice computed tomographic coronary angiography to predict the outcome of percutaneous recanalization of chronic total occlusions. *Am J Cardiol.* 2005;95:240-243.
 111. Werner GS. Use of coronary computed tomographic angiography to facilitate percutaneous coronary intervention of chronic total occlusions. *Circ Cardiovasc Interv.* 2019;12:e007387.
 112. Galassi AR, Sumitsuji S, Boukhris M, et al. Utility of intravascular ultrasound in percutaneous revascularization of chronic total occlusions: an overview. *JACC Cardiovasc Interv.* 2016;9:1979-1991.
 113. Karpaliotis D, Lembo N, Kalynych A, et al. Development of a high-volume, multiple-operator program for percutaneous chronic total coronary occlusion revascularization: procedural, clinical, and cost-utilization outcomes. *Catheter Cardiovasc Interv.* 2013;82:1-8.

10 Bifurcations

ANTONIO COLOMBO AND AZEEM LATIB

INTRODUCTION, 175

SIMPLIFIED GUIDELINES AFTER 20 YEARS OF BIFURCATION STUDIES, 176

Provisional Approach is the Default Strategy, 176

Two Stents Can Be Selectively Implanted as Intention to Treat or Cross-over from the Provisional Approach, 179

Residual Side Branch Stenosis After the Provisional Approach Is Often Not Significant, 179

Kissing Balloon Inflation or High-Pressure Individual (Side and Main Branch) Postdilation Should Always Be Used When Implanting Two Stents and Optionally When Implanting One Stent, 181

Optimal Technique Is a Must especially When Two Stents Have Been Implanted, 182

Stent Thrombosis After Bifurcation Percutaneous Coronary Intervention, 183

AN INDIVIDUALIZED APPROACH TO BIFURCATIONS, 183

THE LEFT MAIN, 184

TECHNICAL ASPECTS OF BIFURCATION PERCUTANEOUS CORONARY INTERVENTION, 185

General Aspects, 185

Provisional Approach, 186

Cross-over to Double Stenting from a Provisional Approach, 188

Elective Double Stenting, 190

Ancillary Devices and Procedures, 203

CONCLUSIONS, 204

INTRODUCTION

A bifurcation coronary lesion is a stenosis involving or adjacent to the origin of an arterial side branch 2 mm or greater in diameter and is composed of a proximal main vessel (PMV) that divides into two smaller branches, the distal main vessel (DMV) and side branch (SB). The stenosis can involve the large branch (main branch [MB]), the smaller branch (SB), or both. Coronary bifurcation lesions have been the subject of several classifications. However, attempts to classify bifurcation lesions suffer all the limitations of coronary angiography (different plaque distribution, presence of calcification, angulation, and extent of disease when evaluated by intravascular ultrasound).¹ Furthermore, these classifications are all anatomic and do not dictate the treatment strategy or prognosis of a specific bifurcation lesion. There are currently at least eight different classifications of bifurcation lesions (Figure 10.1).²⁻⁹ The most important distinction is to divide bifurcation lesions into “true” bifurcations, when the MB and the SB are both significantly narrowed (>50% diameter stenosis) and “non-true” bifurcations, which include all the other lesions involving a bifurcation. Other important elements to consider that are not inherent in the bifurcation classifications include the extent of disease on the SB (limited to the ostium or involving the vessel beyond the ostium), its size (>2.5 mm of reference diameter), the bifurcation angle, disease distribution, and the presence of calcification. In routine practice, the Medina classification is still the most simplified and widely used approach to classify distribution of atherosclerotic plaque at the bifurcation site.⁷ However, as mentioned, the Medina classification does not take into account the size, area of distribution, and lesion length of the branches, which are the most important features that determine decision making. The best way to summarize these three features is to measure the fractional flow reserve (FFR) (physiological summary of all these three features).

Approximately 15% to 20% of percutaneous coronary interventions (PCIs) are performed to treat coronary bifurcations.¹⁰⁻¹² However, PCI for bifurcation disease continues to remain a lesion subset of great interest for interventional cardiologists because it has been known to be technically challenging and has historically been associated with lower procedural success rates and worse clinical outcomes than nonbifurcation lesions.¹¹ This is predominantly related to the variability in anatomy (plaque burden, location of plaque, angle between branches, diameter of branches, bifurcation site), the technical challenges of treating two vessels at the same time when intervention in one of the vessels can negatively impact the other, the numerous technical approaches that could potentially be applied, and the challenges in individualizing the treatment to a specific bifurcation anatomy and patient. Indeed, the trend and much of the available data support simplifying the treatment of bifurcations to that of treating a non-bifurcated segment of the coronary artery. Attempts to reduce the complexity of bifurcation PCI should not be interpreted as a one-technique approach (i.e., single MB stent provisional approach) can be applied to all bifurcations but rather that simple techniques should be used for noncomplex bifurcations, and complex techniques should be reserved for complex bifurcations or as a bail-out for failure or complications during a provisional approach.

It should be remembered that procedural complications and challenges could also occur when performing a simple approach mainly because of acute closure or severe stenosis of the SB. The incidence of acute SB occlusion with main vessel (MV) stenting has been reported at approximately 8% and is associated with increased rates of cardiac death and myocardial infarction (MI).¹³ In fact, the complexity of treating bifurcations relates predominantly to understanding and choosing the correct strategy for managing the SB. The size, anatomy, extent of disease, distribution, and importance of the SB dictate the approach. In some cases, PCI may be avoided completely or

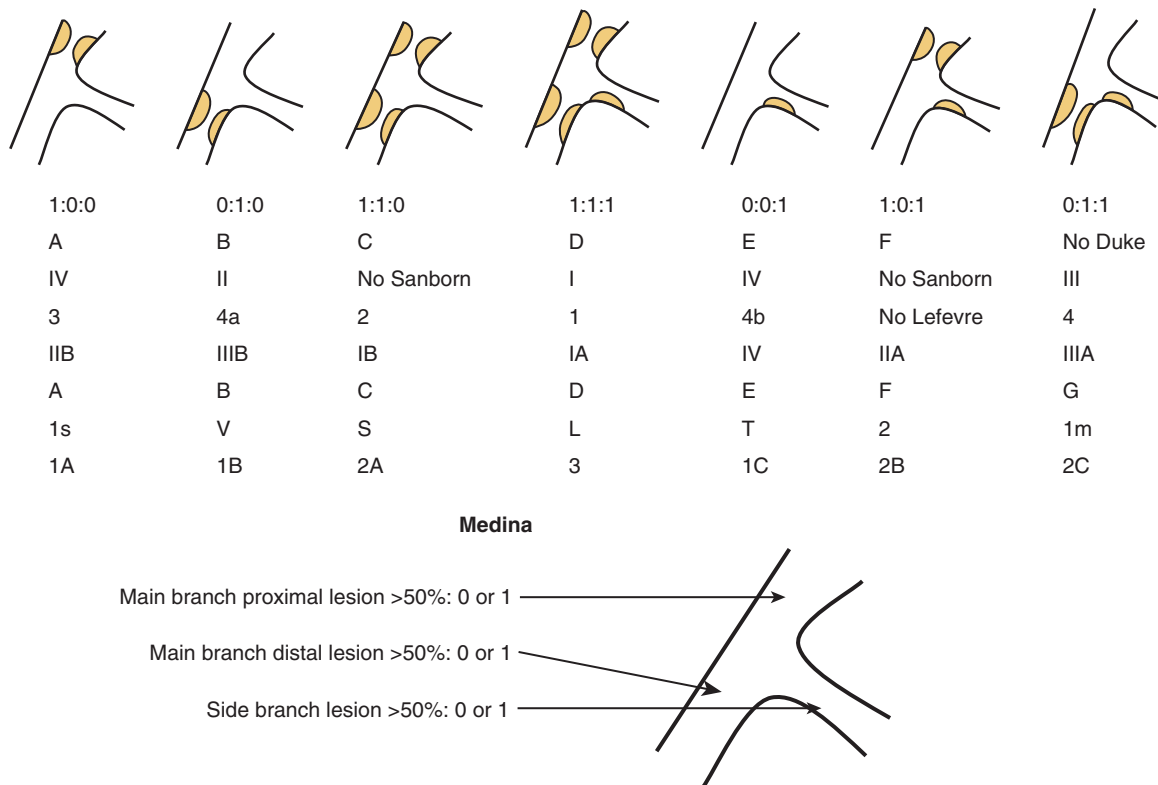


FIGURE 10.1 Classifications of bifurcations according to plaque distribution: Medina,⁷ Duke,² Sanborn,⁵ Lefevre,³ Safian,⁴ SYNTAX,⁹ Movahed,⁸ and Staico-Feres.

contraindicated if the SB cannot be protected. An important point to stress is that the implantation of one single stent on the MB is the most widely used approach at present and should be considered the default approach in most bifurcations, including left main (LM) bifurcations. The presence of SB disease extending beyond the ostium, the larger the size of the SB, and the larger the territory the SB supplies may necessitate the implantation of two stents as intention to treat.

In this chapter, we summarize the important clinical data and give a detailed explanation of all the technical aspects of bifurcation PCI.

SIMPLIFIED GUIDELINES AFTER 20 YEARS OF BIFURCATION STUDIES

Bifurcations have become an area of increased research over the past 20 years. This was spurred by the advent of drug-eluting stents (DESs) and their effectiveness in reducing restenosis, particularly in complex lesions such as bifurcations, which led to numerous bifurcation-specific randomized trials being performed. However, the superiority of DES over bare-metal stents (BMSs) was not evaluated in a specific randomized trial, which seemed unnecessary and unethical because restenosis and revascularization rates were dramatically lower than those seen when bifurcations were treated with BMS.^{14,15} The only randomized data comparing DES and BMS comes from a subanalysis of the SCANDSTENT (Stenting Coronary Arteries in Non-Stress/Benestent Disease) trial, which examined a total of 126 patients with bifurcation lesions treated with

sirolimus-eluting stents (SESs) or BMS.¹⁶ In 55% of the SES cohort and 53% of the BMS cohort, stents were implanted in both branches of the bifurcation. SES implantation was associated with significant reductions in restenosis rates at the MB (4.9% vs 28.3%; $P < .001$) and SB (14.8% vs 43.4%; $P < .001$), as well as major adverse cardiac events (MACEs) (9% vs 28%; $P = .009$) during the 7-month follow-up period. Similarly, registry studies have shown marked reductions in MACE and target lesion revascularization (TLR) rates compared with historical BMS control participants. These reductions occurred irrespective of whether a one-stent (MACE, 5.4% vs 38%; TLR, 5.4% vs 36%) or two-stent (MACE, 13.3% vs 51%; TLR, 8.9% vs 38%) strategy was used.^{15,17} As a result, DESs are the preferred stents for the treatment of coronary bifurcations even in the setting of acute MI or patients at high bleeding risk,^{18,19} and outcomes related to DESs in bifurcations will be discussed henceforth.

Provisional Approach is the Default Strategy

There are now nine randomized studies²⁰⁻²⁸ available comparing a provisional approach of implanting one-DES (1S) in the MB only versus a two-DES (2S) approach of implanting a DES on both the MB and SB of the bifurcation, the results of which are summarized in Table 10.1 and Figure 10.2. It is apparent from these data that routine stenting of both branches offers no clear advantage over a provisional strategy of stenting the MB only with balloon angioplasty of the SB, regarding restenosis in the main or SBs or in repeat bifurcation revascularization. A 2S approach is associated with procedures that are longer with more

TABLE 10.1 Randomized Studies Comparing Provisional Stenting with Elective Double Stenting with Drug-Eluting Stents in Coronary Bifurcations

AUTHOR (YEAR)	AIM	ONE-STENT GROUP										TWO-STENT GROUP										CROSS-OVER FROM ONE TO TWO STENTS	SB STENTED IF:
		PATIENTS (n)	FOLLOW-UP (mo)	ANGIO FU (%)	SIDE BRANCH			RESTENOSIS RATE (%)			ANGIO FU (%)	RVD (mm)	DS (%)	LESION LENGTH (mm)	SIDE BRANCH			RESTENOSIS RATE (%)					
					RVD (mm)	DS (%)	LESION LENGTH (mm)	MB	SB	TLR (%)					ST (%)	MB	SB	TLR (%)	ST (%)				
Colombo et al. ²⁰ (2004)	Both branches vs provisional	85	6	84	2.1	46.2	5.1	4.8	14.2	4.5	0	95	2.1	56.8	5.5	5.7	21.8	9.5	4.7	51.2%	>50% residual stenosis in SB		
Pan et al. ²¹ (2004)	Both branches vs provisional	91	6	87	2.5	64	N/A	2.4	4.9	2.1	0	89	2.5	65	N/A	10.3	15.4	4.5	2.2	2.1%	>50% residual stenosis AND TIMI flow<3		
Steigen et al. ²² (2006)	Crush, culotte, Y vs provisional	413	6	73	2.6	46	6.0	4.6	19.2	1.9	0.5	76	2.6	47	6.4	5.1	11.5	1	0	4.3%	TIMI flow=0 after SB dilatation		
Ferenc et al. ²³ (2008)	Reverse crush vs provisional	202	12	95	2.39	53.1	10.4	7.3	9.4	10.9	1.0	95	2.38	54.4	9.9	3.1	12.5	8.9	2.0	18.8%	>60% stenosis and/or flow-limiting dissection		
Colombo et al. ²⁴ (2009 ⁹)	Crush vs provisional	350	6	86	2.16	61	5.7	6.7	14.7	6.3	1.1	86	2.30	63	5.9	4.6	13.2	7.3	1.7	31%	>50% stenosis and/or flow-limiting dissection		
Hildick- Smith et al. ²⁵ (2010)	Crush, culotte vs provisional	500	6	13	N/A	63	N/A	2.8	2.8	5.6	0.4	17	N/A	68	N/A	4	3.6	7.2	2	3%	>70% stenosis, or flow-limiting dissection or TIMI flow<3		
Chen et al. ²⁶ (2011)	DK Crush vs provisional	370	12	92	2.29	63.4	14.9	9.7	22.2	13	0.5	92	2.29	62.8	15.4	3.8	4.9	4.3	2.2	28.6%	>50% stenosis, or flow-limiting dissection or TIMI flow<3		
Kumsars et al. ²⁷ (2020)	Culotte, crush, T-stenting vs provisional in large SBs	450	24	70	2.33	43	6.4	1.3	20.3	9.2	1.8	68	2.4	49	7.7	1.3	5.2	6.2	1.3	3.7%	TIMI flow<3		
Hildick- Smith et al. ²⁸ (2016)	Culotte vs provisional	200	12	N/A	2.61	54.1	9.7	N/A	N/A	2.9	1.0	N/A	2.72	54.8	10.8	N/A	N/A	1.0	2.1	16%	TIMI flow<3 or 90% ostial ste- nosis or threat- ened Sb closure or flow-limiting dissection		

^aStent thrombosis defined as per definition in study.

Angio, Angiography; DS, diameter stenosis; FU, follow-up; MB, main branch of the bifurcation; N/A, not available or not applicable; one-stent group, bifurcation lesions treated with provisional stent technique; RVD, reference vessel diameter; SB, side branch of the bifurcation; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization; ST, stent thrombosis; two-stent group, bifurcation lesions treated with both branch stenting techniques.



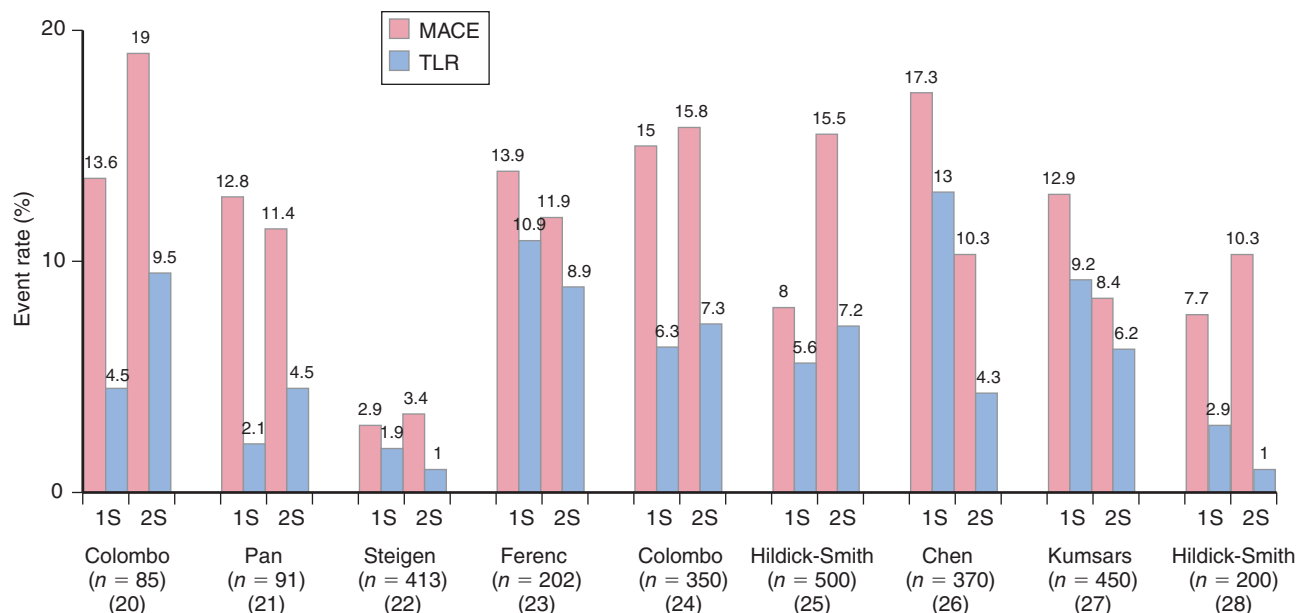


FIGURE 10.2 Clinical outcomes in the seven randomized trials comparing the one-stent (1S) versus two-stent (2S) strategies using drug-eluting stents. MACE, Major adverse cardiac events; TLR, target lesion revascularization.

fluoroscopy time and contrast volumes and a higher rate of procedure-related biomarker release.²² Importantly, none of these studies showed that elective double stenting of the bifurcation is associated with higher revascularization, follow-up MI, or stent thrombosis rates. Interestingly, the most recent of these studies Double Kissing Crush (DKCRUSH-II), is the first and only randomized trial to suggest that double stenting may be superior to provisional stenting and associated with a lower rate of restenosis and repeat revascularization.²⁶ In this study, 370 true bifurcations were randomly assigned to treatment with either provisional stenting or a modification of the crush technique, the double-kissing (DK) crush. The DK crush was associated with a reduction in restenosis, especially of the SB (4.9% vs 22.2%; $P < .001$) and TLR (4.3% vs 13%; $P = .005$) but not in MACE (10.3% vs 17.3%; $P = .07$). How do we reconcile the contradictory findings of the DKCRUSH-II study with those of the other bifurcation studies? In our opinion, this study reconfirms the importance of bifurcation technique and optimization of the final result (in this case a refinement of the standard crush technique) with a 2S approach is directly related to long-term outcomes. Nevertheless, we see no rationale to make a procedure more complex when similar immediate- and medium-term follow-up results can be obtained with a simpler approach.

These randomized bifurcation studies provide us with the evidence that the provisional approach should be the default strategy in most bifurcations. However, we should not incorrectly interpret them as stating that *all* bifurcations must be treated with a provisional approach because complex or high-risk bifurcations were not well represented in these trials. As seen in Table 10.1, patients included in these randomized controlled trials (RCTs) had moderately sized SBs with focal ostial lesions of moderate severity, and patients with long and/or severe SB stenoses or large SBs were largely excluded. Also, other important anatomic features, such as the myocardial territory supplied by the SB,

angle of the SB, and the presence or absence of distal SB disease, were not provided in these trials. In an attempt to resolve these shortcomings, three other randomized trials have been recently published. In the Nordic-Baltic Bifurcation Study IV, Kumsars et al.²⁷ randomized true bifurcations with large SBs (≥ 2.75 mm) and SB lesion lengths up to 15 mm to provisional SB stenting or a 2S approach. A 2S approach was associated with a longer procedure and a nonsignificantly lower rate of MACE at 6 months (2.2% vs 5.5%; $P = .07$) and 2 years (8.4% vs 12.9%; $P = .12$) compared with the provisional approach. Interestingly, the restenosis rate at the SB was significantly higher with simple stenting (20.3% vs 5.2%; $P < .01$). However, again, these data may not be applicable to more complex bifurcations because SBs with lesions larger than 15 mm were excluded.

The European Bifurcation Club Two (EBC-TWO) trial is the most recent randomized study to compare a provisional approach with a 2S approach with culotte stenting. It has randomized 200 true bifurcations (with SBs of >2.5 mm and lesion length >5 mm) to provisional or culotte stenting.²⁸ The rates of final kissing inflation (FKI) were 95% or greater in both groups, and cross-over from provisional occurred in 16%. The MACE and TLR rates at 12 months were similar in both groups (7.7% vs 10.3%; $P = .53$ and 2.9% vs 1.0%; $P = .621$, respectively). Procedure time, x-ray dose, and cost all favored the provisional approach.

Thus, although the default strategy for most bifurcations should be the provisional approach, we should continue individualize decision making based on the patient's individual anatomy because there are bifurcation lesions in which two stents (main and SB stenting) need to be implanted as intention to treat because of the characteristics of the lesion and the distribution of the SB. Indeed, not all bifurcations can be treated with one technique; rather, the technique should be matched to the individual bifurcation anatomy, guided by the available data as well as by personal experience.

Two Stents Can Be Selectively Implanted as Intention to Treat or Cross-over from the Provisional Approach

The distinction between a provisional approach and electively implanting two stents is that in the 1S approach the operator may be willing to accept a suboptimal result in the SB, provided TIMI (Thrombolysis in Myocardial Infarction) flow is normal and the SB has limited clinical relevance regarding territory of distribution. However, how do we define what a suboptimal result in the SB is? It is important to note that a major difference between the nine randomized trials in Table 10.1 was the definition of a suboptimal result in the SB. This definition has a major impact on both the cross-over rate from a 1S to 2S strategy and the restenosis rate in SBs treated with a provisional strategy. In the Sirius Bifurcation study,²⁰ a residual stenosis of greater than 50% in the SB was considered unacceptable, which explains the very high cross-over rate of 51.2%. In contrast, in the Nordic study,²² the residual SB stenosis was irrelevant, and the SB had just to remain open with TIMI greater than 0 flow. This clarifies why the highest (19.2%) SB restenosis rate with a 1S approach was observed in this study. However, in modern practice, we should also acknowledge that physiological restenosis as measured by FFR is clinically more important than angiographic restenosis. Indeed, many angiographic restenoses of SBs will have normal FFR values because of the presence of a focal ostial stenosis, the smaller territory of distribution, and the severity of the stenosis. Although it may be satisfactory to accept a suboptimal result with TIMI 1 flow in a small obtuse marginal branch, such a result is not acceptable when treating a distal LM bifurcation or a bifurcation involving a large diagonal branch. In examining the recent CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents),²⁹ Bad Krozingen,²³ and DKCRUSH-II²⁶ bifurcation studies, a more realistic figure is that in about 20% of bifurcations treated with a provisional strategy, a second stent will have to be implanted on the SB.

The major difference between an elective 2S approach and cross-over to 2S from a 1S approach is that in the former, the SB is stented first because of the risk of closure or because the SB is clinically relevant and has significant disease. This may be appropriate in complex bifurcations in which the risk of SB occlusion with MB stenting is high such as those with more severe disease, longer lesions, wider angles that are difficult to rewire, or that have a dissection after predilation. Although the presence of large plaque burden at the bifurcation can be associated with SB ostial deterioration or occlusion after MB stent implantation even in the absence of baseline SB ostial disease, the presence of SB disease increases this risk. Indeed, several studies have shown that the risk of SB occlusion increases with the severity of SB disease. Aliabadi et al.³⁰ showed that the risk of SB occlusion was 14% to 27% for SBs with ostial stenosis greater than 50% as compared with 1% to 4% in SBs with minimal or no disease. Furakawa et al.³¹ showed that the risk of SB deterioration (final TIMI ≤ 2) was more common in SBs with ostial disease of 50% or greater (20.8% vs 6.1%; $P = .049$) and in longer lesions.

Similarly, Chaudhry et al.³² demonstrated that the risk of SB compromise increased with increased SB ostial stenosis severity (for every 10% increase in SB stenosis severity, the risk of SB compromise increased by 23%) and calcification (46% vs 26%; $P = .06$). A criticism of these studies is that they are old and may not reflect current advances in techniques and devices. However, Hahn et al.¹³ have recently studied the predictors of SB occlusion that occurred in 187 (8.4%) of 2227 bifurcation lesions. On multivariable analysis, independent predictors of SB occlusion were preprocedural percent diameter stenosis of the SB of 50% or greater and proximal MV greater than 50%, SB lesion length and acute coronary syndromes. Of 187 occluded SBs, flow was restored spontaneously in 26 (13.9%) and by SB intervention in 103 (55.1%) but not in 58 (31.0%).

However, an important change that has occurred in clinical practice is the understanding that in SBs without high-risk features, the operator could cross over to 2S if necessary (i.e., significant residual stenosis or flow-limiting dissection). The reasons for cross-over depend on the size, the severity of residual disease, and the myocardial territory of the SB. All these features are best assessed by a physiological evaluation as discussed in the next section. A number of bifurcation techniques can be performed as cross-over as discussed later in the chapter, but we prefer the T-stenting and small protrusion (TAP) technique because of its simplicity and because it is associated with excellent long-term outcomes. We evaluated the long-term outcomes of this technique in 95 patients who underwent SB stenting with the TAP as a cross-over from the provisional approach. TAP stenting was successful in all patients and was associated with a TLR rate of 5.1% and no stent thrombosis at 3-year follow-up.³³

Residual Side Branch Stenosis After the Provisional Approach Is Often Not Significant

Because the provisional approach has now become the gold standard, important questions remain about the cause, significance, and management of a residual stenosis at the ostium of the SB. There has been considerable debate as to whether the appearance of a new stenosis or aggravation of an existing stenosis at the SB ostium after MB stenting is caused by plaque shift or carina shift. Historically, it has been suggested that SB compromise during PCI is the result of snowplowing of plaque over the SB ostium, that is, plaque shift, especially in bifurcations with a shallow SB angle. However, pathologic evaluation and intravascular ultrasonography (IVUS) studies have shown that although atherosclerosis develops frequently at the bifurcation, it is often located opposite to the flow divider (i.e., opposite to the origin of the SB). This led to the hypothesis that has subsequently been demonstrated on IVUS that SB compromise after MB stenting may be caused by carina shift rather than plaque shift. (See Figure 10.3 for an example of carina shift.)

A recent study by Koo et al.³⁴ of IVUS evaluation after MB stent implantation showed (1) a significant increase in the vessel and lumen volume index in both the proximal and distal segments of the MB, (2) a significant decrease in the plaque volume index in the proximal segment of the

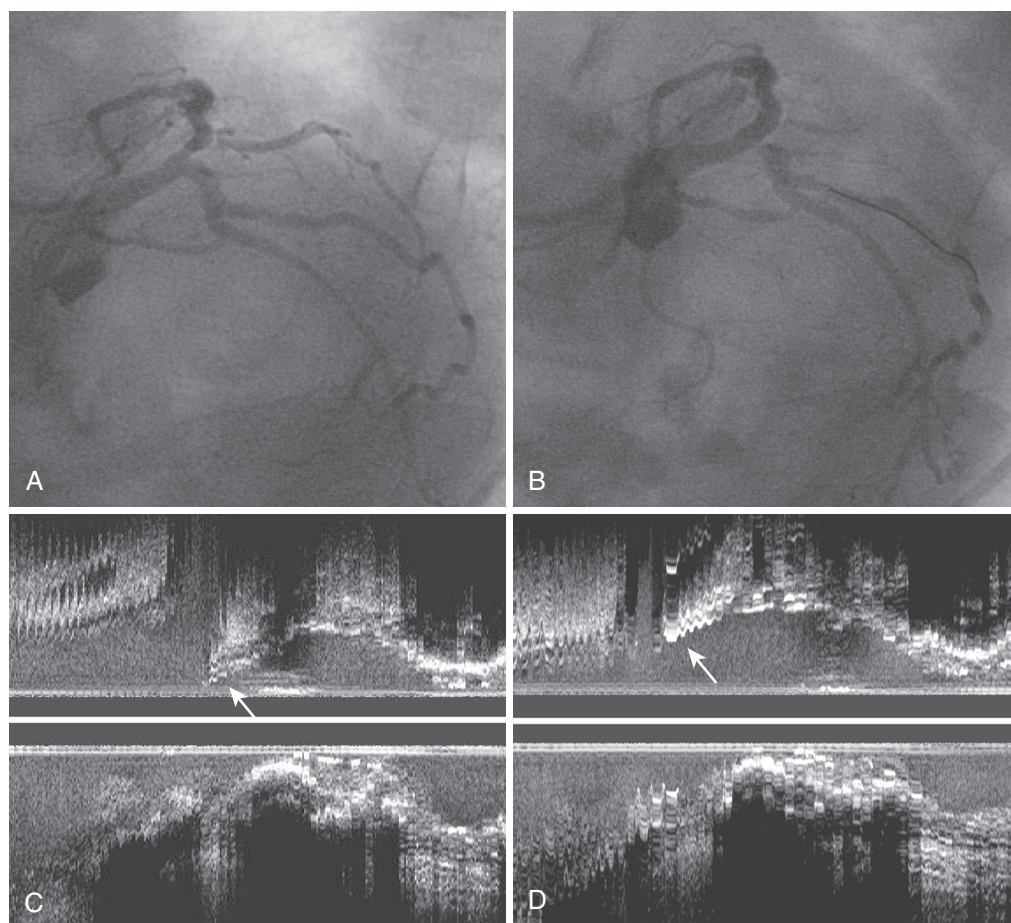


FIGURE 10.3 Example of carina shift. Angiographic (A) and intravascular ultrasonography (IVUS, B) images of a left main coronary artery (LMCA) bifurcation showing an unobstructed circumflex ostium (left) before stenting and an ostial narrowing after stent implantation from the LMCA to left anterior descending coronary artery (LAD). The IVUS images demonstrate there is an alteration in the location and geometry of the carina (arrows). The carina is shifted toward the side branch (SB), and this shift results in an eccentric luminal narrowing of the SB ostium.

MB, and (3) no change in the plaque volume index in the distal segment of the MB after stenting. These results suggest that the lumen increase in the distal MB is primarily due to enlargement of the vessel and not plaque shift, supporting the concept that part of the luminal narrowing of an SB after stenting the MB is explained by carina shift. However, in the proximal MB, the plaque area changed significantly after stent implantation, particularly in the region closest to the ostium of the SB. Although, plaque shift to the SB ostium was not observed directly, these data provide indirect evidence of plaque shift from the proximal segment of the MB into the SB ostium after MB stent implantation. Thus, both plaque shift from the MB and carina shift contribute to the creation or aggravation of an SB ostial lesion after MB stent implantation. Carina shift will occur if the bifurcation angle is less than 90 degrees when full MB dilation is performed. Although carina shift may be prevented by selecting the MB stent diameter according to the DMV diameter, the operator should not compromise optimal MB dilation to avoid carina shift.

Additionally, there appears to be increasing evidence that trying to get an optimal angiographic result with minimal residual stenosis in the SB may not be physiologically important. This concept is especially important in smaller SBs, where the majority of angiographically significant SB lesions have been demonstrated to be not functionally

significant by FFR analysis.³⁵ Koo et al.³⁵ performed FFR measurements on 94 jailed SB lesions after stent implantation on the MB. No lesion with a 50% or greater and less than 75% stenosis had an FFR less than 0.75. Among 73 lesions with greater than 75% stenosis, only 20 lesions were functionally significant, and among those with greater than 95% stenosis, only 14 of 25 had FFR values less than 0.75.³⁵ Furthermore, smaller SBs are less likely to result in angina if a residual stenosis is left untreated or if restenosis occurs.^{36,37} Indeed, FFR may be the most physiological and evidence-based method to guide the decision as to whether a jailed SB with a residual stenosis should be treated. Koo et al.³⁵ evaluated the FFR in 91 jailed SBs (reference vessel diameter [RVD], 2.3 ± 0.3) after MB stenting and if treatment based on whether the FFR was functionally significant would impact on clinical outcomes. Only 30% of all jailed SB lesions had an FFR less than 0.75 with 96% of all SBs successfully accessed with pressure wire. The functionally significant SB lesions were treated with kissing balloon inflation, which resulted in 92% (23 of 25) of these lesions having an FFR greater than 0.75. At 6-month follow-up, 48% of SB lesions had a stenosis greater than 75%, but only 8% had a functionally significant FFR. However, this approach is more time consuming, costly, at times technically challenging (rewiring jailed SB with a pressure wire) and was not associated with better clinical outcomes than an

angiography-guided approach (MACE, 4.6% vs 3.7%; $P = .7$). Nevertheless, this study does confirm that kissing inflation is effective in treating functionally significant SB stenoses caused by carina or plaque shift and that many moderately sized jailed SBs with a residual stenosis may be treated conservatively or only with kissing inflation rather than stenting.

Kissing Balloon Inflation or High-Pressure Individual (Side and Main Branch) Postdilation Should Always Be Used When Implanting Two Stents and Optionally When Implanting One Stent

Final kissing balloon inflation (FKBI) allows SB ostium treatment and apposition of the MB stent struts on the SB ostium. It also enables correction of stent distortion and inadequate apposition in the MB.^{38,39} However, FKBI increases procedural complexity and may result in stent ovalization, proximal dissection when balloons are inadequately positioned, and even suboptimal deployment of the proximal stent segment. There is uncertainty as to whether FKBI is mandatory when a provisional approach is used. Theoretically and from benchmark studies, FKBI has the advantage of opening stent struts that potentially can scaffold the SB ostium, correcting MB stent distortion and proximal expansion caused by SB balloon dilation through the MB struts, and facilitating future access to the SB. Despite the favorable carinal modification of FKBI, it may cause elliptical distortion of the PMV stent and can potentially induce stent malapposition.⁴⁰ There is also concern that stenting across a bifurcation without opening the stent struts into the SB results in “malapposed” struts across the SB ostium that are not endothelialized.

There are now two clinical studies that address whether FKBI should be routinely performed after the provisional approach. In the Nordic-Baltic Bifurcation Study III, 477 patients with bifurcation lesions undergoing main vessel stenting were randomized to FKBI ($n = 238$) or no FKBI ($n = 239$).⁴¹ The 6-month MACE rates were 2.1% and 2.5% ($P = 1.0$) in the final kissing and no-final kissing groups, respectively. At 8 months, the rates of angiographic restenosis of the entire bifurcation lesion were 11.0% versus 17.3% ($P = .11$), 3.1% versus 2.5% in the MB ($P = .68$) and 7.9% versus 15.4% in the SB ($P = .039$) in the final kissing versus no final kissing groups, respectively. The lower restenosis rate in the SB was attributable to the efficacy of FKBI in reducing angiographic restenosis in true bifurcation lesions, in which the SB restenosis rate was 7.6% versus 20.0% ($P = .024$) in the final kissing and no final kissing groups, respectively.

Similar results were obtained in the Cordoba & Las Palmas (CORPAL) Kiss study that compared the incidence of 1-year clinical events in patients with bifurcation lesions who had been treated with a simple approach who were randomized to either a simultaneous FKBI or an isolated SB balloon after dilation.⁴² The angiographic data and immediate results were also similar in both groups. TLR was required in seven patients (3%): five from the FKBI group and one from the non-FKBI group. The incidence of MACE at 1 year (death, TLR, or acute MI) was similar in both groups:

11 (9%) from the FKBI group and 7 (6%) from the non-FKBI group ($P =$ not significant).

The Thueringer bifurcation study (THUEBIS) randomized patients to mandatory SB intervention or intervention only in the event of TIMI flow less than 2.⁴³ Final SB TIMI 3 flow was similar between both groups, with no difference in 6-month MACEs or need for SB PCI during follow-up. Finally, the large Coronary Bifurcation Stenting (COBIS-III) registry of 2194 patients showed no difference at 5 years in target lesion failure rates between 1685 patients treated with a simple cross-over strategy compared with 509 patients treated with an additional SB-opening procedure.⁴⁴ Similarly, some data suggest that the PMV distortion caused by FKBI may result in increased MB events. The COBIS registry identified a higher incidence of MACE and TLR in patients undergoing FKBI, with most TLR occurring in the MB (hazard ratio [HR], 3.39; 95% confidence interval [CI], 1.86–6.19 for the FKBI group).⁴⁵ A meta-analysis of five randomized studies showed that FKBI significantly reduced SB restenosis (odds ratio [OR], 0.44; 95% CI, 0.30–0.64) at the cost of increased MB restenosis (OR, 2.96; 95% CI, 1.74–5.01).⁴⁶ These studies support the simple approach of only MB stenting without routine FKBI in nontrue bifurcation lesions. However, in true bifurcation lesions that are treated with the provisional approach, FKBI should be considered because it is associated with improved angiographic outcomes in the SB. The FKBI-induced PMV stent distortion can potentially be minimized by using shorter balloons to reduce the overlap length of kissing balloons in PMV and by repeating the proximal optimization technique (POT) after FKBI to remold the proximal segment of the stent.⁴⁷ Also, as previously mentioned, FKBI is very effective in improving the FFR in functionally significant SB lesions. Finally, it should be remembered that FKBI should only be performed in bifurcations in which the SB is suitable for stenting if dissection occurs. Indeed, to reduce the risk of SB injury, compliant balloons should be avoided because they may result in underexpansion of the MB stent and significant overexpansion of the SB ostium.⁴⁸ Indeed, in a study by Mylotte et al.,⁴⁸ systematic kissing balloon postdilation with noncompliant balloons was associated with favorable procedural results, a low (6%) rate of cross-over to SB stenting, and a promising 12-month MACE rate of 4%.

In contrast to the provisional approach, FKBI has been repeatedly demonstrated to reduce late loss and restenosis, especially at the SB ostium, and has now become standard in the performance of all double-stenting techniques.^{24,49-51} FKBI is not only important to correct stent distortion and expansion^{38,39} but is also especially important in fully expanding the proximal stent in particular when treating the left main coronary artery (LMCA) bifurcation because the diameter of the distal LMCA is usually much larger than the diameters of the left anterior descending coronary artery (LAD) and left circumflex coronary artery (LCX). The initial data supporting the importance of FKBI with a 2S approach come from bench testing by Ormiston et al.^{38,52} with three different stent platforms (BX Velocity, Cordis, a Johnson & Johnson Company; Express II, Boston Scientific; and Driver, Medtronic) using the crush technique. FKBI with appropriately sized SB and MB after dilation was needed to fully expand the stent at the SB ostium, to widen gaps between stent struts overlying the SB (facilitating subsequent

access), and to minimize stent distortion. The importance of FKBI with the crush technique has also been confirmed in a clinical study that demonstrated significant reductions in restenosis (11.1% vs 37.9%) and late loss (0.32 vs.0.52 mm) of the SB in the group treated with FKBI.⁵⁰ Similarly, a subanalysis of the CACTUS trial showed that FKBI was associated with better angiographic results and lower MACE rates when complex stenting was performed, and similar results were observed when using a more simple provisional SB stenting technique.²⁴

However, it is imperative that FKBI with a 2S approach be performed with an optimal technique for it to be effective, including the use of adequately sized noncompliant balloons (i.e., a diameter equal to greater than the implanted stent, high-pressure inflation, two-step kissing inflation, and correction of proximal distortion by the overlapping balloons with a short noncompliant balloon). The two-step kissing inflation consists of high-pressure balloon inflation in the SB before performing the true FKBI at medium pressures and is particularly important when performing the crush technique. In the culotte technique, we advise that a three-step kissing inflation is performed in which the FKBI is preceded by high-pressure inflation of each branch of the culotte. Ormiston et al.⁵³ have recently demonstrated through imaging of bench deployments that (1) recrossing the crushed stent for kissing after dilation, the most difficult part of the procedure, is technically easier with mini-crush than with classical crush; (2) traditional one-step FKBI leaves considerable residual metallic stenosis that may not be visible on angiography and may predispose to thrombosis because of eddy currents, stasis, altered shear stress, and foreign body presence; and (3) SB ostial coverage and residual stenosis by metal struts is significantly reduced by two-step FKBI (Figure 10.4).⁵³

Optimal Technique Is a Must especially When Two Stents Have Been Implanted

The requirement for double stenting is dependent on the complexity of the bifurcation that the interventional cardiologist is willing to treat, the importance of the bifurcation to that patient, and the willingness to accept a suboptimal angiographic result in the SB. Thus, in treating simple bifurcations with small to moderately sized SBs, the rate of double stenting may be as low as 5% to 10%. In more complex bifurcations with large and extensively diseased SB, this may be as high as 15% to 20%, with the highest rate of double stenting in the LMCA bifurcation ($\leq 30\%$). Thus, there will still be situations where the operator needs to implant a stent in both branches of the bifurcation electively or as a cross-over from the provisional approach. If properly performed, there appears to be no evidence of harm to the patient, and there may even be an advantage over the provisional approach in certain situations. However, when implanting two stents, the operator takes on the responsibility of ensuring optimal performance of the technique because the 2S approach is less forgiving and may give to a suboptimal result, which may result in restenosis or stent thrombosis. In this regard, a number of important technical factors may contribute to optimizing outcomes when performing 2S techniques such as high-pressure SB inflation, the use of noncompliant balloons, selection of correct balloon size for FKBI, the DK crush technique, and the use of intravascular imaging.¹¹ Despite the absence of a dedicated IVUS study, we strongly favor using IVUS to evaluate and to improve the final result when implanting two stents. An exception to this approach is present when the TAP technique is used. This approach may make IVUS evaluation difficult.

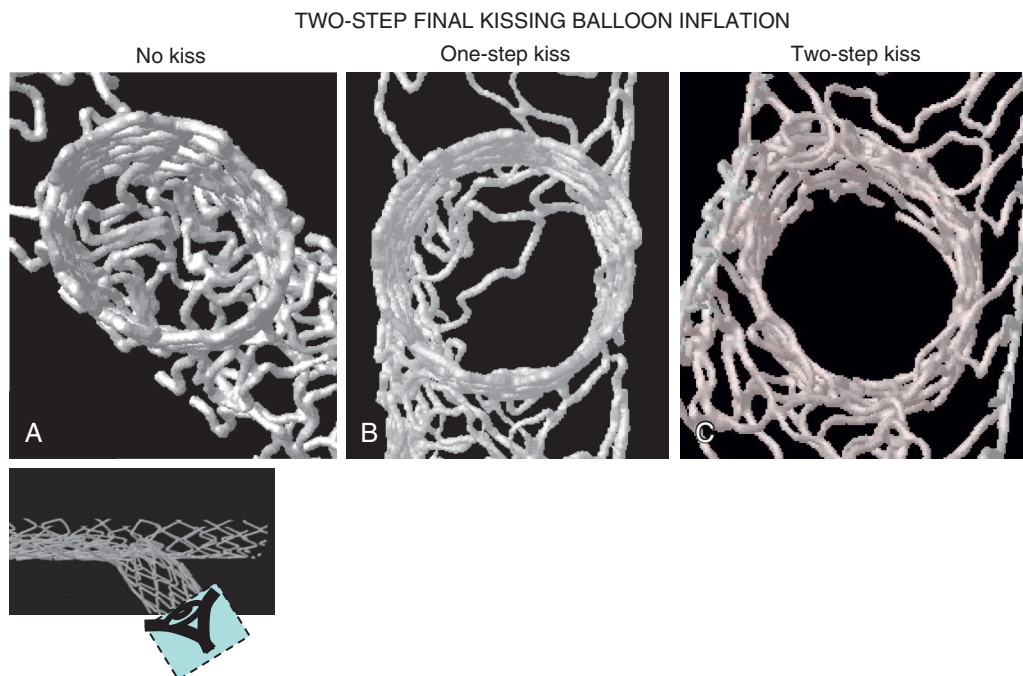


FIGURE 10.4 Bench-top imaging of the ostium of the side branch (SB) after the crush technique with no final kissing balloon inflation (FKBI, **A**), classical one-step FKBI (**B**), and the recommended two-step FKBI (**C**) that results in the best opening of struts toward the SB.

Stent Thrombosis After Bifurcation Percutaneous Coronary Intervention

Stenting bifurcation lesions with DES has been identified as a risk factor for stent thrombosis.⁵⁴ However, data from the individual randomized trials discussed already have not demonstrated an increased risk when using two stents versus one stent.^{10,19-23} Similarly, two meta-analyses of the randomized trials performed have not demonstrated an increased risk of stent thrombosis with double-stenting techniques.^{55,56} Finally, long-term data from the Nordic Bifurcation Study have shown similar rates of definite stent thrombosis with provisional and double stenting (3% vs 1.5%; $P = .31$) at 5 years.⁵⁷ However, the use of two stents may be associated with an increased risk of stent thrombosis in the setting of acute MI.⁵⁸ Furthermore, it appears that stent thrombosis at coronary bifurcations is associated with a higher in-hospital and long-term mortality rates than stent thrombosis at nonbifurcation lesions.⁵⁹ This higher mortality rate is at least partly explained by a larger area of myocardium at risk among patients with bifurcation stent thrombosis. There is currently no convincing evidence to suggest that we should refrain from using DESs in bifurcations or that a 2S strategy is associated with a greater risk of stent thrombosis. However, we should make every attempt to prevent stent thrombosis when DESs are implanted in bifurcations. This requires attention to the technical aspects of the procedure, optimization of stent implantation, and dual antiplatelet therapy for at least 12 months. Despite these statements, we should take into consideration the fact that implanting two stents always demands more attention and expertise to obtain the best result in both the MB and SB.

AN INDIVIDUALIZED APPROACH TO BIFURCATIONS

The objective of bifurcation PCI is to end the procedure with both branches open and an optimal result in the MB. However, bifurcations vary not only in anatomy (plaque burden, location of plaque, angle between branches, diameter of branches, bifurcation site) but also in the dynamic changes in anatomy during treatment (plaque shift, carina shift, dissection). As a result, no two bifurcations are identical, and there is no single strategy that can be applied to every bifurcation. Thus, the more important issues in bifurcation PCI are selecting the most appropriate strategy for an individual bifurcation and optimizing the performance of this technique.

Selection of the best strategy requires accurate assessment of lesion severity, calcification, distribution, extension, and presence of concomitant disease by the combination of clinical characteristics, angiography, intravascular imaging, and functional evaluation. This will result not only in the appropriate patients being selected for double stenting, which is more complex, time consuming, and labor intensive than provisional stenting, but will also reduce the risk of complications. The major factors that need to be assessed and taken into account when the operator is deciding between provisional stenting and elective double

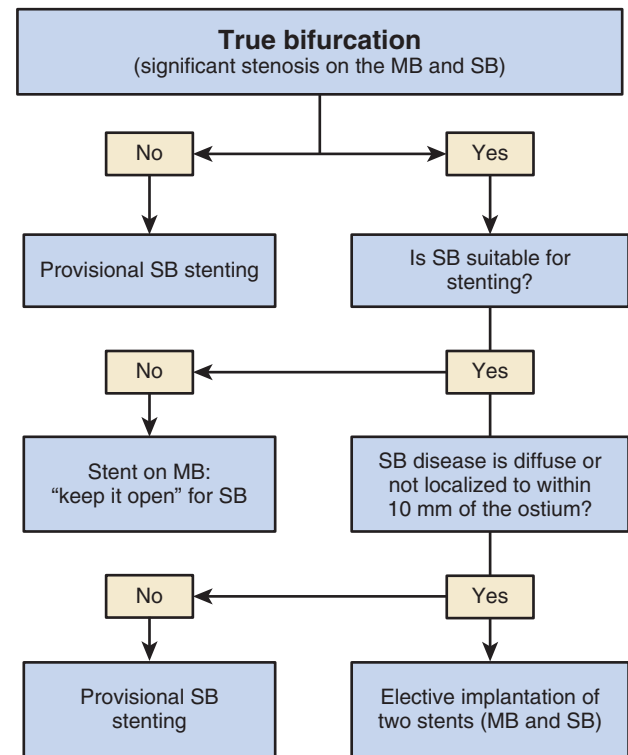


FIGURE 10.5 A proposed algorithm for treating coronary bifurcations. This approach to bifurcation stenting is based on whether both branches have significant disease, the diameter of the side branch (SB), and the extent of disease in the SB. MB, Main branch.

stenting are described next. Although each of these factors is discussed separately, there is usually a combination of these factors present. An individualized approach to treating a bifurcation (Figure 10.5) is dictated by the SB through evaluating the following factors:

1. *Importance of SB preservation for the patient and for their specific anatomy:* The territory of viable myocardium supplied by the SB and risk of SB occlusion is usually the most important factor when evaluating the bifurcation approach.
2. *Distribution of disease:* An important distinction is whether the disease at the bifurcation only involves one branch of the bifurcation or if it extends into both branches.
3. *Size and territory of distribution:* The size of the branch is not considered in isolation but in combination with the severity and length of disease. In general, we would not stent SBs that are smaller than 2.5 mm unless they are long with a somewhat large territory of distribution or the branch is in danger of occlusion. SBs longer than 73 mm in length by computed tomography are most likely to supply 10% or more of fractional myocardial mass.⁶⁰
4. *Extent of SB disease:* The severity and length of disease in the SB is are probably the most common reasons for performing double stenting rather than provisional SB stenting. Focal ostial SB disease should be treated with a provisional approach. However, if the SB is large (≥ 2.5 mm), supplies a relatively large territory of myocardium, and has significant disease that extends 10 to 20 mm or more from the ostium, we would favor a double-stenting



technique from the outset. Also, the result after SB pre-dilation is another important factor in deciding whether to continue with a provisional approach or shift to a double-stenting technique.

5. *Bifurcation angle*: The bifurcation angle is the angle between the MB and SB distal to the bifurcation. The bifurcation angle has an influence on the accessibility of the SB and may frequently be a reason for initially stenting the SB. A wide angle may make initial wiring of the SB difficult and may also impede recrossing into the SB with a wire, balloon, or stent after MB stenting. However, the decision to electively implant a stent on the SB should be made only after wire insertion, which may favorably modify this angle. An acute bifurcation angle is a predictor of SB occlusion during MB stenting; that is, the more acute the angle, the higher the risk of plaque shift, compromise of the ostium, and SB occlusion.^{6,61,62}
6. *Presence of concomitant distal disease in the SB*: If the ostium is nondiseased but there is distal disease close to the ostium that can be covered by a long stent from the MB, we would prefer double stenting. However, if the distal disease cannot be treated with the MB stent and requires a second stent to be implanted distally, we prefer implanting the distal stent first if possible and then treating the bifurcation. This approach avoids difficulty later in passing a stent through stent struts at the bifurcation.

The DEFINITION II (Two-Stent vs. Provisional Stenting Techniques for Patients With Complex Coronary Bifurcation Lesions) trial showed that when using strict criteria similar to these to define bifurcation complexity, a systematic two-stent approach was associated with better clinical outcomes (TLF, 6.1% vs 11.4%; $P = 0.019$) in complex bifurcation lesions, largely driven by an increase in target-vessel MI (7.1% vs 3%; $P = 0.025$) and clinically driven TLR (5.5% vs 2.4%; $P = 0.049$) in the provisional approach group. In the provisional group, we cannot exclude the role of technical aspects to explain the high incidence of MIs and the “oculostenotic reflex” to trigger SB revascularizations at the time of angiographic follow-up.

THE LEFT MAIN

The LM bifurcation differs from non-LM bifurcations in that:

- Larger area of myocardium at jeopardy, there is less room for error during the procedure; the vessels are larger, the SB is as important as the MB regarding both the size and territory of distribution, and the operator is less likely to accept a suboptimal result in the SB.
- Large and highly variable diameter of proximal MB (i.e., LM) with a mean reference diameter of about 5 mm (range, 3.5–6 mm) and diameter can be significantly larger than the distal MB.
- SB is usually the LCX, which is angulated, making it difficult to wire and deliver stents. The LCX is a significant SB with a large reference diameter and area of distribution (supplies >10% of myocardium in >95% of cases).
- LCX ostium appears to have a high rate of restenosis even after DES implantation, which may be related to shear stress; extreme angulation; negative remodeling;

increased movement during cardiac contraction; stent deformation, and higher rates of fibrosis, calcification, and stent underexpansion.^{63,64}

- Only bifurcation where the proximal MB originates directly from the aorta, thus increasing complexity of stenting and guide catheter interaction and leading to a higher risk of wiring below stent struts and longitudinal stent deformation.
- Large and highly variable bifurcation angle of 70 to 80 degrees.
- Coronary calcification and the need for lesion modification are common.
- LM trifurcations may be seen in up to 10% of cases.

Two randomized studies have evaluated a provisional versus double-stenting approach in LM bifurcation with slightly conflicting data. The DK-CRUSH V randomized 482 patients with true distal LM to provisional or DK crush.⁶⁵ The LM bifurcations included in this study were fairly complex with calcification in more than one-third and SB lesion length longer than 10 mm in 50%. SB stenting in the provisional group was high and performed when suboptimal results were present after FKBI (including a residual DS >75%, type B dissection, or TIMI flow grade <3). The primary endpoint, target lesion failure, was significantly increased with the provisional approach compared with DK crush (10%–7% vs 5.0%; $P = .02$) as well as higher rates of target vessel MI (2.9% vs 0.4%; $P = .03$) and definite or probable stent thrombosis (3.3% vs 0.4%; $P = .02$). At 3 years, TLF remained worse with provisional stenting (16.9% vs 8.3%; $P = .005$), with significantly more target vessel MI, TLR, and stent thrombosis.⁶⁶

European Bifurcation Club Left Main Trial (EBC MAIN) was a European randomized study that compared provisional to systematic double stenting (Culotte or T/TAP) in 467 patients.⁶⁷ SB lesion length was only an average of 7 mm, and SB stenting was performed in 22% of provisional cases. MACE at 12 months was similar between the provisional and two-stent groups (14.7% vs 17.7%; $P = .34$), with no difference in individual endpoints. These results seem discordant, especially because the patients treated were more complex in DK-CRUSH V with high SYNTAX scores (31 vs 23) and longer mean SB lesion lengths (16 vs 7 mm). Also, the operators in DK CRUSH V were very experienced high-volume operators, as noted by the requirement to participate in the study (i.e., ≥ 300 PCIs/year for 5 years, including at least 20 LMCA PCIs per year). However, these data still do require validation by other studies.

Our approach to LM bifurcations is very similar to other bifurcation lesions as previously described in this chapter. The provisional approach should be the default in the majority of bifurcations. However, we have a slightly lower threshold for implanting an SB stent for a suboptimal result after provisional but avoid implanting a LCX stent for residual stenosis unless it is greater than 70% or associated with a positive FFR. We previously routinely performed FKBI when performing a provisional approach on LM bifurcations, but this has been challenged by a subanalysis of the Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial that showed FKBI is not associated with improved outcomes at 4 years.⁶⁸ Regarding double stenting,

this approach may especially be important in complex LM bifurcations, especially with very angulated and calcified LCXs, and in patients with depressed left ventricular function. Regarding which technique, the DK crush is the technique with the most clinical data for LM,^{66,69,70} and we strongly recommend FKBI after all double-stenting techniques. Lesion preparation with speciality balloons, lithotripsy, and atherectomy and elective hemodynamic support is used more commonly in LM bifurcations. Intracoronary imaging is highly recommended, and many experts would say mandatory in LM bifurcations.

TECHNICAL ASPECTS OF BIFURCATION PERCUTANEOUS CORONARY INTERVENTION

General Aspects

Guiding Catheter

Most bifurcation lesions should be treated via a 6-Fr guiding catheter because a provisional strategy will be used most of the time. Furthermore, cross-over to a 2S approach from provisional and most elective double-stenting techniques can also be performed with a 6-Fr guiding catheter. However, in very complex bifurcations or trifurcation lesions where multiple (more than two) guidewires will be placed or a 2S technique such as the classical crush or V-stenting is required, we recommend placing a 7- or 8-Fr guiding catheter. If two stents are needed and a 6-Fr guiding catheter is used, some limitations need to be known: (1) the two stents can only be inserted and deployed sequentially; (2) when performing T-balloon stenting, step crush or TAP, the stent should be advanced into the SB first and then the balloon to the MB; and (3) the standard crush, V, or kissing stents technique cannot be performed unless a guiding catheter of 7 or 8 Fr is used.

Vascular Access

We have no preference as regards to femoral or radial access for treating bifurcations. Even complex bifurcations can be treated via the radial approach providing that guide catheter support is adequate.⁷¹ In cases in which

large guide catheters are required, a 7-Fr guide catheter can usually be inserted via 7-Fr radial slender sheaths, or sheathless guide catheters can be used.

Wiring Both Branches of the Bifurcation and Jailed Guidewires

Two wires should be placed in most bifurcations, and the SB wire should be “jailed” in the majority after deployment of the stent on the MB. This approach of wiring both branches during bifurcation stenting is important in protecting the SB from closure caused by plaque shift, carina shift, or stent struts during MB stenting. Even SBs with minimal disease may occlude during MB stenting (Figure 10.6 and Video 10.2). There has been some debate as to whether placing a wire in the SB can protect it from closure after MB stenting. A recent study has finally confirmed that the jailed wire in the SB is associated with flow recovery of SBs that occlude after MB stenting (74.8% vs 57.8%, $P = .02$).¹³ A COBIS III registry substudy also showed jailed SB wires are associated with a lower rate of final SB occlusion after MB stenting in patients with severe stenoses at the SB or MB.⁷² Protecting SBs with guidewires to prevent their closure is important because SB compromise may be consequential. Occlusion of SBs larger than 1 mm can be associated with 14% incidence of MI,⁷³ and SB (≥ 2 mm) compromise during a provisional approach can be associated with a large periprocedural myocardial infarct.³² The jailed SB wire not only protects it from closure but also facilitates rewiring of the SB (if SB postdilation or stenting or final kissing inflation is needed or if the SB occludes) by widening the angle between the MB and SB, by acting as a marker for the SB ostium, or by changing the angle of SB take-off.^{36,39,55,74} Finally, in the case of SB occlusion, the jailed wire can be used to reopen the SB by pushing a small balloon between the stent and the wall of the vessel. There is no need to remove the jailed wire during high-pressure stent dilation in the MB. It is preferable to avoid jailing hydrophilic guidewires because there is a risk of removing the polymer coating. Accurate handling of the guiding catheter to prevent migration into the ostium



FIGURE 10.6 A critical stenosis on the mid left anterior descending coronary artery (LAD) with minimal disease of the diagonal ostium (A; Video 10.1). The operator placed a wire in the LAD only and stented across the diagonal ostium, which occluded despite minimal disease (B; see Video 10.2). An SB wire may have prevented closure or at least facilitated reopening of the vessel.



of the coronary vessel allows removal of the jailed wire. Difficulty removing a jailed wire can be overcome by advancing an over-the-wire balloon or microcatheter to the proximal stent edge to better transmit traction onto the trapped segment.

Difficult Side Branch Access

Safe guidewire placement in the MB and SB is the first step to a successful bifurcation PCI procedure. In some cases of complex bifurcation anatomy with wide SB take-off angles (≥ 90 degrees) or severe disease at the bifurcation, wiring the SB may be extremely challenging and if not properly performed could result in dissection of the SB ostium and acute closure. Indeed, an inability to wire the SB may be a reason not to perform bifurcation PCI or to abort the procedure because the risk to lose the SB will be too high considering the size and distribution of the branch (typically an angulated circumflex artery). A number of technical tips may help in the situation when the SB cannot be wired with a workhorse coronary guidewire⁷⁵:

1. Antegrade wiring with a change of guidewire to a stiffer or hydrophilic polymer-coated wire, making a single wide bend or double bend shape, with the support of a microcatheter. Stiffer wires enhance precision and torque control and are usually our first option when a workhorse wire fails. Hydrophilic or polymer-jacket wires are usually our last option because although they may shorten and facilitate SB wiring, they have a greater risk of wire perforation or subintimal navigation (especially if the SB has been injured by balloon dilation).
- ▶ 2. Pullback wiring technique (Figure 10.7 and Videos 10.3 and 10.4): A guidewire with a smooth, large distal bend

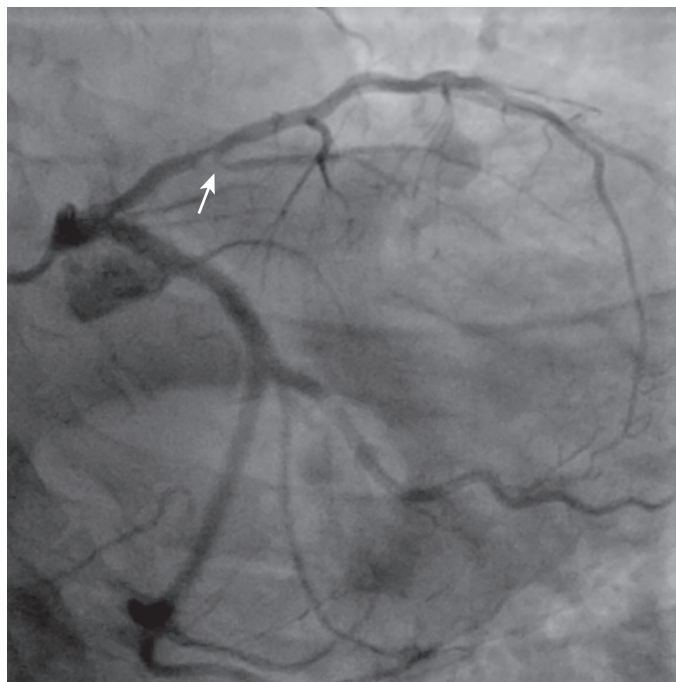


FIGURE 10.7 Angiography demonstrating a severe stenosis of the proximal left anterior descending coronary artery (LAD) involving the diagonal ostium that has a hairpin bend origin (see Video 10.3) and was very difficult to wire with standard techniques. A pullback wiring technique as demonstrated in Video 10.4 was used the wire this angulated side branch.

or loop is advanced into the distal MB and pulled back to the bifurcation. Because of the hooklike bend, the distal tip of the guidewire engages the SB ostium; gentle counterclockwise rotation advances the wire in the SB.

3. Reverse wire technique: A polymer-jacket hydrophilic guidewire with a round shape (reverse bend) at about 3 cm from the distal tip is advanced distal to the bifurcation with a dual-lumen microcatheter. The guidewire and microcatheter are pulled back to the bifurcation, and owing to the hairpin bend, the distal tip engages the SB. A gentle counterclockwise rotation advances the guidewire in the SB. At this stage, the reverse guidewire is usually exchanged for a conventional wire using a microcatheter.
4. Venture wire control catheter or SuperCross angled tip microcatheters (Teleflex) enable the guidewire to be directed toward the SB after active or passive deflection of the catheter tip. The deflectable catheter is tracked over a guidewire just distal to the SB ostium, and the guidewire is withdrawn into the deflectable catheter. The SuperCross catheter tip changes from a straight tip to its preformed curve (45, 90, or 120 depending on which catheter is selected), whereas the Venture catheter is actively deflected to the required angulation. When the catheter is adequately orientated to the SB ostium, the guidewire can be easily advanced.
5. Rotational atherectomy on the MB with the intent to remove the plaque that prevents entry toward the SB and facilitate SB wiring
6. MB predilation with the rationale that the plaque modification and a favorable plaque shift will facilitate access toward the SB. This is usually a last resort because it may result in occlusion of the SB.

Each of these options has its rationale and specific anatomical indication. The operator's experience and the clinical scenario will direct the selection of the best strategy. Usually, the final option is the one frequently used when wiring has failed and is usually effective.

Provisional Approach

We divide the provisional approach into two different strategies depending on the size, extent of disease, and importance of the SB. Making this distinction at the outset saves time and clarifies the operator's objective regarding the expected final result, especially if the stenosis of SB is aggravated by MB stenting. A 6-Fr guiding catheter is usually preferred for the provisional approach.

1. The SB is not suitable (too small) for stenting or clinically irrelevant and has ostial or diffuse disease: The strategy proposed in these bifurcations is the "keep it open" strategy, which is performed as follows:
 - a. Wire both branches.
 - b. Dilate the MB if needed but not the SB.
 - c. Stent the MB and leave the wire in the SB.
 - d. Perform postdilation of the MB with the jailed wire in the SB.
 - e. Do not rewire the SB or postdilate the SB.

This "jailed wire" strategy allows protection of an SB that may not require treatment but where the need to maintain patency is important. This strategy can be used as a stand-alone technique or as part of the

provisional strategy when the operator may need to eventually dilate or stent the SB. This approach of just “keep it open” for the SB was the strategy used in the provisional stenting group of the Nordic Study.²²

2. The SB is suitable for stenting and the SB has minimal disease or disease at the ostium only: In these bifurcations, the provisional strategy is used. This strategy is quick, safe, and easy to perform and has been shown to be associated with results comparable to a more complex approach. The provisional approach is performed as follows:

- a. Wire both branches.
- b. Predilate the MB and the SB as required; many SBs without significant disease or calcification do not require predilation.
- c. Stent the MB and perform a POT, leaving the SB wire in place. If the angiographic results in MB and SB are satisfactory, the procedure is complete, and the SB wire jailed behind the MB stent struts can be gently removed.
- d. Rewire the SB and then remove the jailed wire. Recrossing through the distal strut (“carina strut”) after MB stenting is strongly recommended because it creates better SB scaffolding than proximal crossing. In our experience, recrossing into the SB through the MB stent struts is usually possible using a conventional guidewire or the Rinato-Prowater or Sion Blue/Black wires (Asahi Intecc). The recommended technique for wire recrossing is to first advance the guidewire distally through the MB, preferably with a curve, to avoid passing under the MB stent struts. The wire is then pulled back with the tip facing the SB ostium and grating the stent struts. When the tip reaches the first cell covering the ostium, it engages the SB and with a gentle rotation is advanced into the SB. The jailed wire in the SB should always be left in place as a marker until complete recrossing has been done or MB stenting has been completed, including high pressure stent deployment or postdilation. The operator should refrain from removing the jailed wire when difficulties are encountered to rewire the SB. The POT should be liberally used to facilitate rewiring of the SB.
- e. SB balloon dilation and FKBI are done with moderate pressure (8 atm) in the SB until the balloon is fully expanded. FKBI is mandatory if the SB is dilated through the MB stent struts to correct MB stent distortion and expansion.^{38,39} FKBI should only be performed in bifurcations in which the SB is suitable for stenting if dissection occurs.
- f. If the result remains unsatisfactory (suboptimal result, FFR <0.75, plaque or carina shift with >75% residual stenosis or TIMI <3; in an SB ≥ 2.5 mm) or SB balloon dilation is complicated by a flow-limiting SB dissection, then SB stenting should be performed.

Proximal Optimization Technique

To prevent carina shift, the MB stent diameter should be selected according to the diameter of the DMV. Inflation of a short, bigger balloon just proximal to the carina corrects

the underdeployment of the proximal part of the MB stent. As a result, the original anatomic configuration of the bifurcation is restored in compliance with the Muray and Finet law.⁷⁶ POT also changes the orientation of the SB ostium and projection of struts in the SB ostium, thus facilitating wire recrossing into the most distal strut, balloon crossing, and if necessary, a stent in the SB. POT is especially useful in bifurcation lesions with a large SB because a marked difference in the diameter of the proximal and distal MB is observed. Appropriate positioning of the balloon for POT is important because a position that is too distal may result in carina shift and proximal stent malapposition, whereas a position that is too proximal may result in edge dissection and incomplete expansion at the SB ostium. Thus, it is also important to ensure that short 6- to 8-mm noncompliant balloons are available and that a stent length is chosen that will allow sufficient stent in the PMV to allow a POT without causing proximal edge dissections. The correct position of the POT balloon is with the distal balloon shoulder immediately proximal to the carina, which may be different depending on balloon design and manufacturer because balloons have different distances between the shoulder and marker. Chevalier et al.⁷⁷ have shown in a retrospective study that POT is associated with a reduction in target lesion failure at 12 months.

Final Kissing Balloon Inflation

Selection of appropriately sized noncompliant balloons for FKBI is crucial. The diameter must match that of the two distal branches. The balloons must be sufficiently short to avoid inflation outside the stent in the MB and in disease-free areas in the SB. The use of noncompliant balloons prevents overexpansion at the SB ostium, vessel injury, and dissection while ensuring adequate MB stent expansion.⁴⁸ In cases in which POT has not been performed, FKBI may optimize the proximal segment of the MB. During FKBI, we inflate a balloon in the MB first and then the SB balloon to achieve strut projection in the ostium. The pressure applied depends on the persistence of a waist on the balloon. In bifurcations with large proximal MBs, some operators prefer reperforming the POT to correct ovalization of the proximal MB stent caused by the kissing balloons. Sequential balloon inflation (side, main, side or only side, main) has also been proposed as an alternative to FKBI.⁷⁸

Technical Tips for the Provisional Approach

1. Always wire both branches.
2. Predilate the SB only if there is severe disease or the risk of occlusion after MB stenting.
3. The MB stent is selected according to the distal MB diameter.
4. The SB wire should be jailed behind the MB stent.
5. POT is used to optimize proximal MB stent deployment and facilitate wire recrossing.
6. Recross the MB through the distal strut.
7. Do not remove the jailed wire until recrossing or MB stent optimization has been performed.
8. FKBI is not mandatory but probably advantageous in true bifurcations with significant residual SB stenosis (>70%) or am FFR less than 0.75.

9. High-pressure proximal stent inflation using a short noncompliant balloon should be considered for correction of possible proximal stent distortion after FKBI.

Cross-over to Double Stenting from a Provisional Approach

If the SB result remains unsatisfactory after MB stenting and balloon dilation of the SB ($>75\%$ residual stenosis, dissection, TIMI flow grade <3 or FFR <0.75 in an SB ≥ 2.5 mm), SB stenting should be performed. SB stenting can be performed with the TAP, reverse crush, or culotte techniques followed by kissing balloon inflation.

T Technique

This technique (Figure 10.8) is most frequently used to shift from provisional stenting to stenting the SB. The T technique consists of advancing a second stent into the SB (after adequate dilation of the MB stent struts). The stent is positioned at the ostium of the SB, trying to minimize any possible gap. A second kissing balloon inflation is also performed. The T technique is best suited when the angle between the MB and the SB is close to 90 degrees because in narrow angles, it is impossible to fully cover the ostium without protruding into the MB. Thus, we have replaced this technique with the TAP.

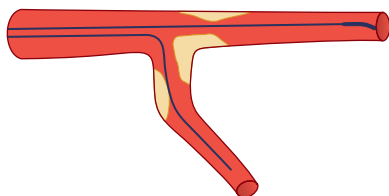
T Stenting and Small Protrusion

The TAP technique (Figure 10.9) is a modification of the T-stenting technique and is based on an intentional minimal protrusion of the SB stent within the MB.³³ This technique can be described as follows:

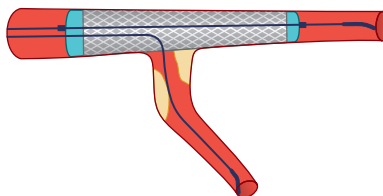
1. A second stent is positioned in the SB with the aim to protrude as minimally as possible into the MB (1 or 2 mm), thus ensuring complete coverage of the ostium of the SB.
2. A balloon is advanced in the MB.
3. The SB stent is deployed as usual (≥ 12 atm), while the uninflated balloon remains parked in the MB at the bifurcation.
4. The SB stent balloon is pulled backward slightly, ensuring that it is still within the MB stent. Subsequently, simultaneous FKBI is performed using the SB balloon and the previously positioned MB balloon at high pressure.
5. The SB is deflated last, and both balloons are deflated and removed.

The SB stent now completely covers the ostium. Despite some concerns about stent protrusion in the MB, in our experience, we have been able to perform IVUS in the MB and SB and when needed to advance additional stents distally in the MB and in the SB. The TAP has become our preferred technique when we need to implant a stent in the SB during a provisional approach because it is easy to

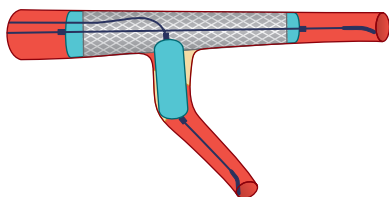
1. Wire both branches and predilate if needed.



2. Stent the MB, leaving a wire in the SB. The stent in the MB can be deployed at high pressure.

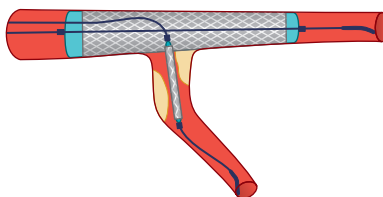


3. Rewire the SB passing through the struts of the MB stent, remove the jailed wire, dilate toward SB, and perform final kissing inflation.



Assuming that the result is suboptimal.

4. Advance the stent into the SB with no MB protrusion and deploy the stent.



5. Perform final kissing inflation after advancement of a balloon in the MB. If needed, use a new balloon for the SB.

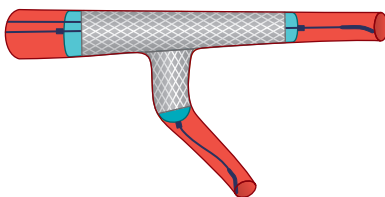
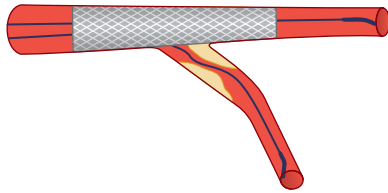
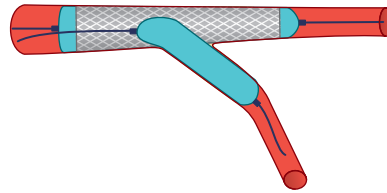


FIGURE 10.8 A schematic representation of the provisional T-stenting technique. MB, Main branch; SB, side branch.

1. Leave a wire in the SB and deploy a stent in the MB.

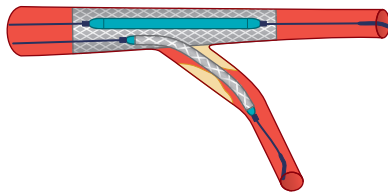


2. Rewire the SB passing through the struts of the MB stent, remove the jailed wire, dilate toward SB, and perform final kissing inflation.

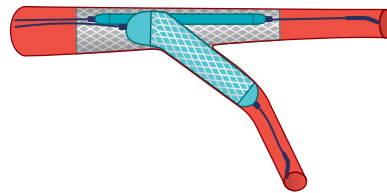


Assuming that the result is suboptimal.

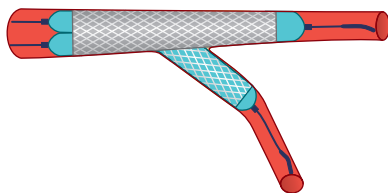
3. Advance stent into SB, ensuring coverage of the ostium with minimal protrusion (1–2 mm) into the MB and place a non compliant balloon in the MB stent.



4. Deploy the SB stent as usual while the MB balloon remains uninflated.



5. Pull back the SB balloon and simultaneously inflate both balloons to perform final kissing.



6. To ensure optimal final results at the SB ostium, the SB balloon must be deflated last when kissing inflation is finished.

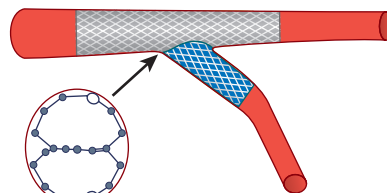


FIGURE 10.9 A schematic representation of the T-stenting and small protrusion technique. MB, Main branch; SB, side branch.

perform, does not require recrossing of the SB struts to perform FKBI, and appears to be associated with good long-term outcomes.³³

Reverse Crush

This technique (Figure 10.10) should be used as a cross-over approach with the intent to minimize any possible stent gap between the MB and SB stents in conditions in which the angle between the MB and the SB is acute (usually <60 degrees). In this situation, the TAP technique may result in excessive protrusion when attempting to fully cover the ostium of the SB. The reverse crush can be performed using a 6-Fr guiding catheter according to the following steps:

1. A second stent is advanced into the SB and left in position without being deployed.
2. A balloon sized according to the diameter of the MB and shorter than the stent already deployed is advanced in the MB and positioned at the level of the bifurcation with attention paid to stay inside the stent previously deployed in the MB.
3. The stent in the SB is retracted about 1 to 2 mm into the MB and deployed. The deploying balloon is removed, and an angiogram is obtained to verify the absence of any distal dissection and the need of an additional stent. If such is the case, then the wire from the SB is

removed, and the balloon in the MB is inflated at high pressure (≥ 12 atm).

4. SB struts are recrossed with a wire and a balloon. The balloon is sized to the SB reference diameter and inflated at high pressure (1220 atm), and final kissing inflation is performed (i.e., two-step kissing balloon inflation).

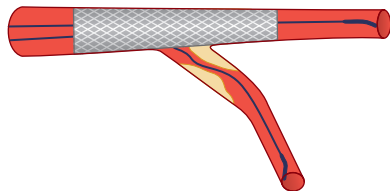
Provisional or Reverse Culotte

The provisional culotte technique (Figure 10.11) can be proposed as a provisional SB stenting strategy in Y-shaped angulated bifurcation lesions without a large discrepancy in size between the MB and SB.⁷⁹ This technique can be described as follows:

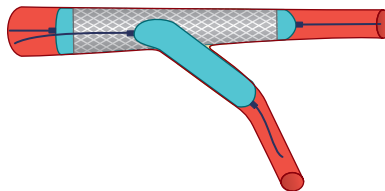
1. After MB stenting, a second stent is advanced in the SB protruding into the MB to overlap minimally (miniculotte) with the proximal part of the MB stent and expanded.
2. A POT is performed to fully appose the SB stent struts in the PMV before MB rewiring.
3. The MB is rewired through the protruding SB stent struts, the jailed MB wire is removed, and a balloon is advanced into MB across the protruding struts and dilated.
4. Finally, kissing balloon inflation is performed.

Both the reverse crush and culotte require a second recrossing of stent struts. As a result, they have been

1. Leave a wire in the SB and deploy a stent in the MB.

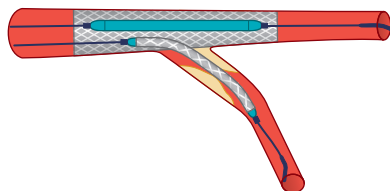


2. Rewire the SB passing through the struts of the MB stent, remove the jailed wire, dilate toward SB, and perform final kissing inflation.

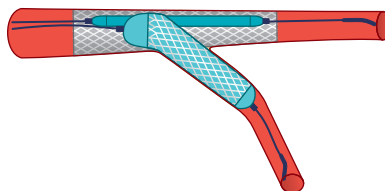


Assuming that the result is suboptimal.

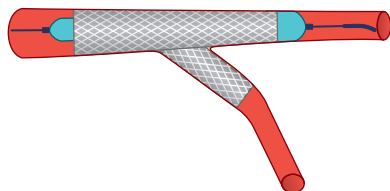
3. Advance the stent into the SB, ensuring coverage of the ostium with minimal protrusion (1–2 mm) into the MB and place a non compliant balloon in the MB stent.



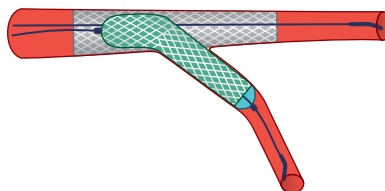
4. Deploy the SB stent as usual while the MB balloon remains uninflated.



5. Remove the SB balloon and ensure that no distal dissection is present before removing the SB wire. Inflate the MB at high pressure to crush the SB stent.



6. To ensure optimal final results at the SB ostium, the SB balloon must be deflated last when kissing inflation is finished.



7. Perform final kissing balloon inflation.

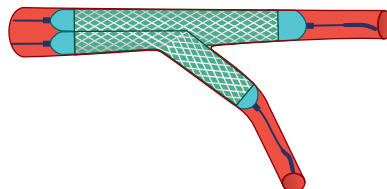


FIGURE 10.10 A schematic representation of the reverse crush technique. MB, Main branch; SB, side branch.

superseded by the TAP when the bifurcation angle is unfavorable.

Elective Double Stenting

Correct patient selection for elective double stenting requires accurate assessment of lesion severity, distribution, and extension, as well as the presence of concomitant disease.^{11,80,81} The decision to perform double stenting depends predominantly on the SB and should generally be reserved for true bifurcations with SBs that (Figure 10.12):

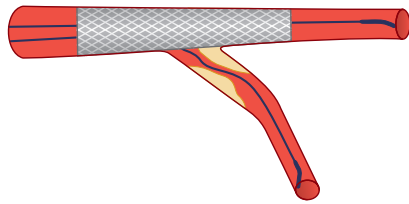
- Are relatively large in diameter (≥ 2.5 mm) and territory of distribution (Figure 10.13)
- Have severe disease that extends well beyond the ostium (i.e., ≥ 10 –20 mm; Figure 10.14)
- Have an unfavorable angle for recrossing after MB stent implantation (Figure 10.15)

We do not consider these variables in isolation, but there is usually a combination of these factors present that dictates the decision to electively perform double stenting. The only situation when we would perform double stenting as intention to treat for a nontrue bifurcation with a nondiseased ostium is if there is distal disease close to the ostium that can be covered by a long stent from the MB. We should emphasize that the decision to implant a second stent may also be made at an intermediate time, such as after wire insertion that may favorably modify the bifurcation angle or following predilation of the MB and SB. However, a timely taken action will affect the result, help save time and cost, and lower the risks of complications.

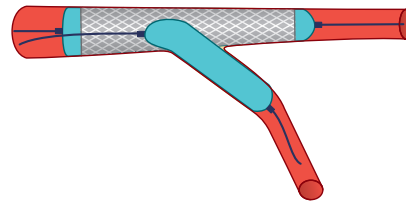
Selecting a Double-Stenting Technique

There are limited data comparing different double-stenting bifurcation techniques, and there is no unequivocal

1. Leave a wire in the SB and deploy a stent in the MB.

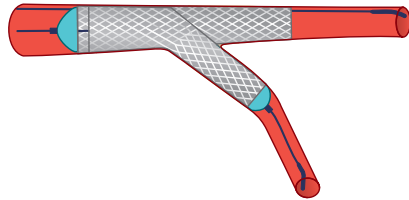


2. Rewire the SB passing through the struts of the MB stent, remove the jailed wire, dilate toward the SB, and perform final kissing inflation.

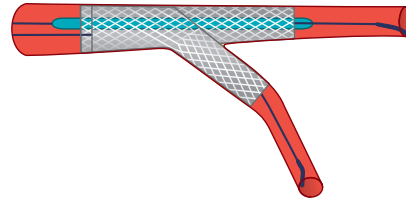


Assuming that the result is suboptimal.

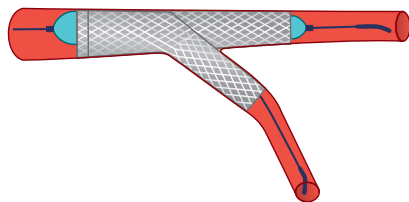
3. Advance the stent into the SB to overlap with the proximal part of the MB stent and deploy.



4. Rewire the MB, remove the jailed MB wire, and advance a balloon in the MB.



5. Perform high-pressure MB dilation.



6. Perform high-pressure inflation toward each branch followed by final kissing balloon inflation.

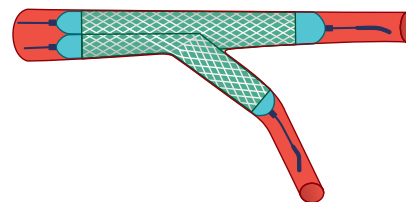


FIGURE 10.11 A schematic representation of the reverse culotte technique. MB, Main branch; SB, side branch.

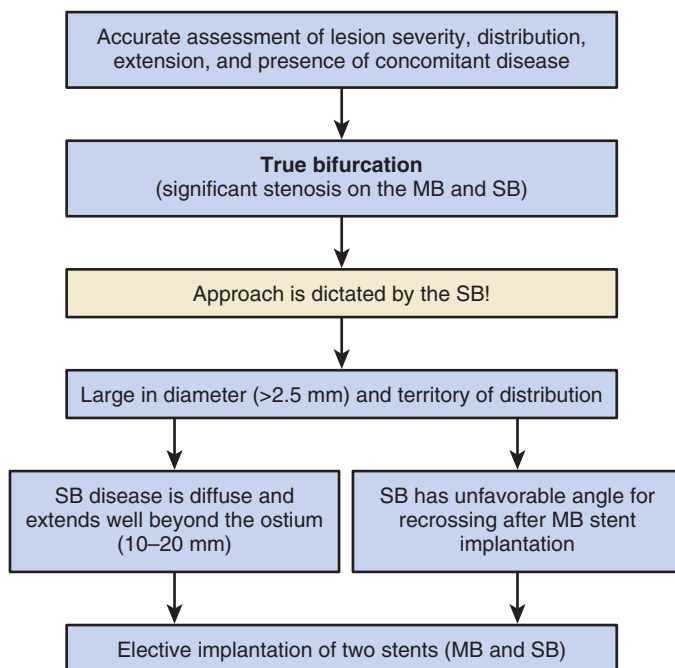


FIGURE 10.12 A proposed algorithm for when to perform elective double stenting. The approach is dictated by the size, angle, and severity of disease of the side branch (SB). MB, Main branch.

evidence demonstrating the superiority of one technique over others. The Nordic Stent Technique Study was the first randomized trial comparing two different double-stent techniques that result in complete coverage of the SB ostium. In this study, 424 patients were randomized to either crush or culotte stenting using SESs (77% of which were true bifurcation lesions).⁸² At 6-month clinical follow-up, there were no significant differences between the two groups in terms of death, MI, or revascularization (4.3% for crush vs 3.7% for culotte; $P = .87$). Procedure and fluoroscopy times and contrast volumes were also similar in the two groups. However, there was a trend for higher incidence of periprocedural MI (15.5% for crush vs 8.8% for culotte; $P = .08$). Angiographically, there was a trend toward less in-segment restenosis (6.6% vs 12.1%; $P = .10$) and significantly reduced in-stent restenosis after culotte stenting (4.5% vs 10.5%; $P = .046$). The relevance of this angiographic finding is unclear and may be explained by the lower rate of FKBI in the crush group (85% vs 92%; $P = .03$) as well as the lack of two-step FKBI when performing crush stenting. Chen et al.⁶⁹ randomized 419 distal LM bifurcation lesions to double stenting with the DK crush or culotte techniques in the DKCRUSH-III study. Only true bifurcation lesions were treated, and FKBI was performed in 99.5% of both groups. Procedural and fluoroscopy times

SB DIAMETER AND TERRITORY

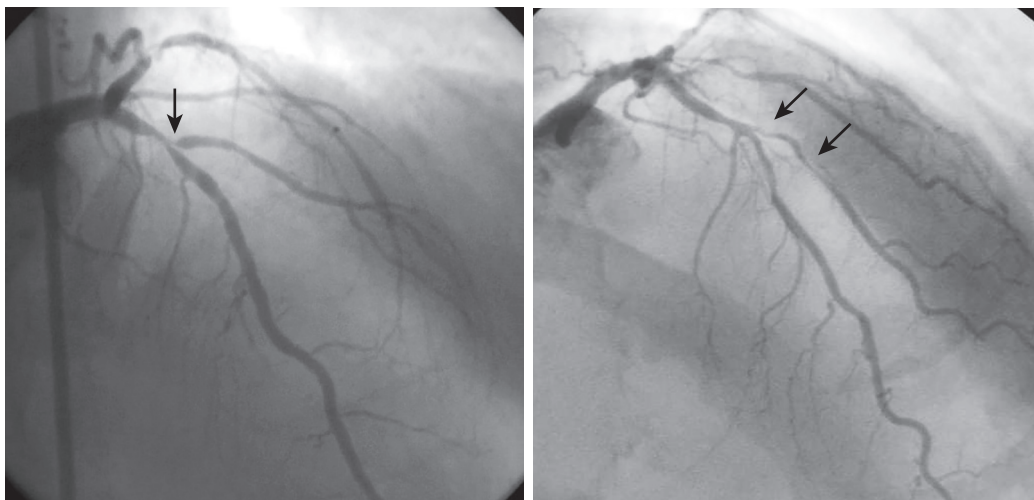


Small with diffuse disease → keep it open

Large SB with large territory → two stents

FIGURE 10.13 Angiographic examples of two left anterior descending coronary artery diagonal bifurcations showing side branches of different sizes and territories of distribution. SB, Side branch.

EXTENT OF SB DISEASE



Focal ostial disease → provisional

Diffuse disease → two stents

FIGURE 10.14 Angiographic examples of two left anterior descending coronary artery (LAD) diagonal bifurcations demonstrating side branches (SBs) with different severities and extents of disease.

were similar, but contrast volume was higher in the DK crush group. At 12-month follow-up, the culotte group has a significantly higher MACE rate (16.3% vs 6.2%; $P = .001$), mainly driven by increased TVR (11% vs 4.3%; $P = .016$) and TLR (6.7% vs 2.4%; $P = .037$), compared with the DK group. Also, restenosis in the SB was higher after culotte stenting (12.6% vs 6.8%; $P = .037$). Definite stent thrombosis rates were 1.0% in the culotte group and 0% in the DK group ($P = .248$).

As a result of these contradictory findings and other large RCTs, we cannot recommend one technique over another, and certainly not all bifurcations can be treated with a single technique. As summarized in [Figure 10.16](#), the selection of the double-stenting technique is based on the

stability of the patient, the anatomy of the bifurcation, and the familiarity and competence of the operator with a specific technique. Important anatomic factors that need to be considered include:

- **Diameter of the two branches** ([Figure 10.17](#) and [Videos 10.5 to 10.8](#)): If the diameters are similar, then culotte or mini-crush should be done, but if there is a large discrepancy between the proximal MB and SB, then mini-crush is preferred.
- **Bifurcation angle** ([Figure 10.18](#) and [Videos 10.9 to 10.12](#)): T stenting and culotte are preferred when the angle is greater than 70 degrees because the crush technique is associated with a high risk of stent malapposition in the SB. Culotte or crush is preferred with angles less than

BIFURCATION ANGLE



Difficult to access SB. Access may be even more challenging or even impossible after MB stenting

FIGURE 10.15 Angiographic example of an unfavorable bifurcation angle (arrow) in which elective double stenting would be indicated. MB, Main branch; SB, side branch.

70 degrees, although T stenting should be avoided because it does not provide complete coverage of the SB ostium.

- *Extent of disease in the MB proximal to the carina* (Figure 10.19 and Videos 10.13 and 10.14): If minimal, then V stenting may be preferred, especially in large proximal SBs.
- *Severity of the ostial SB stenosis* (does it require aggressive pre dilation?)
- *Presence of dissection in MB and SB after predilation* (Figure 10.20 and Videos 10.15 to 10.17): If a dissection is present in both branches of the bifurcation, we prefer the D- crush technique because it ensures immediate patency of both branches compared with the culotte, in which recrossing stent struts into a dissected branch may be challenging and result in vessel closure.
- *Complex bifurcations involving large territories or emergencies* (Figure 10.21 and Videos 10.18 to 10.23):

When dealing with complex bifurcations involving large territories or during emergency situations, when it is crucial to maintain optimal patency of both branches, we recommend the V-stenting or mini-crush techniques. We strongly believe that optimal performance of a double-stenting technique and optimization of the final result is more important than which technique is selected and is what determines clinical outcomes. Important technical factors that may contribute to optimizing outcomes when performing two-stent techniques include FKBI, high-pressure SB inflation, the use of noncompliant balloons, selection of the correct balloon size for FKBI, and the use of IVUS.¹¹

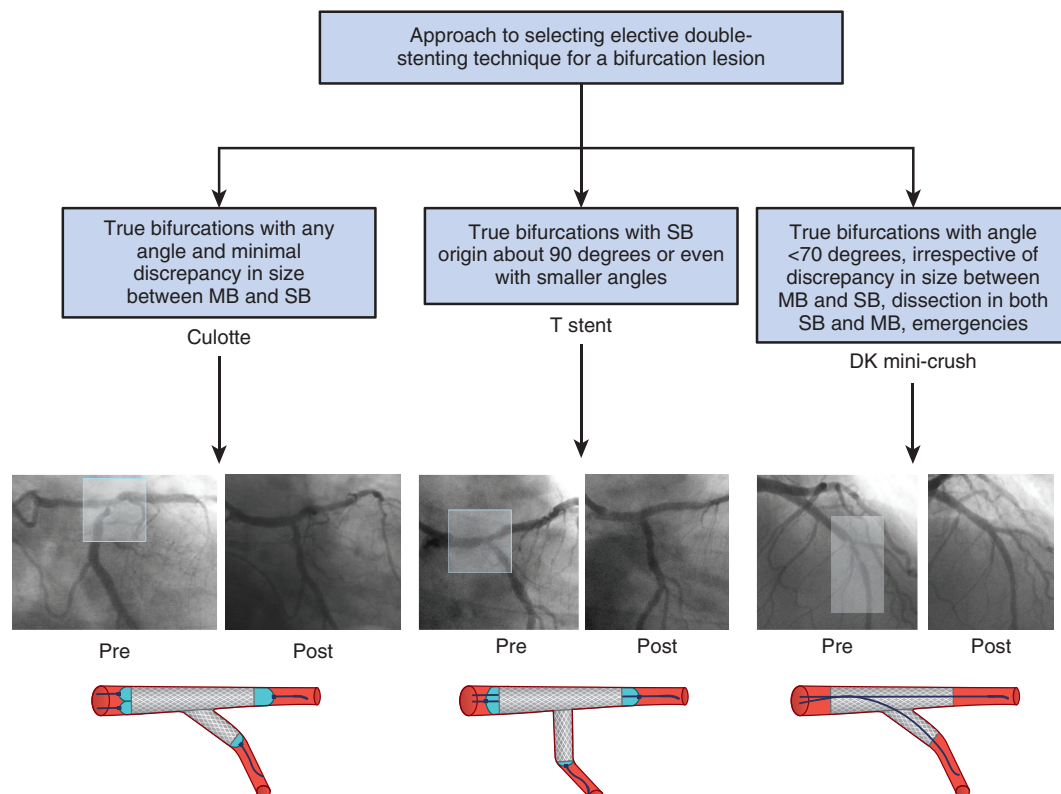


FIGURE 10.16 Algorithm summarizing how to select a double-stenting technique based on anatomy. MB, Main branch; SB, side branch.

DISCREPANCY BETWEEN MB AND SB SIZE

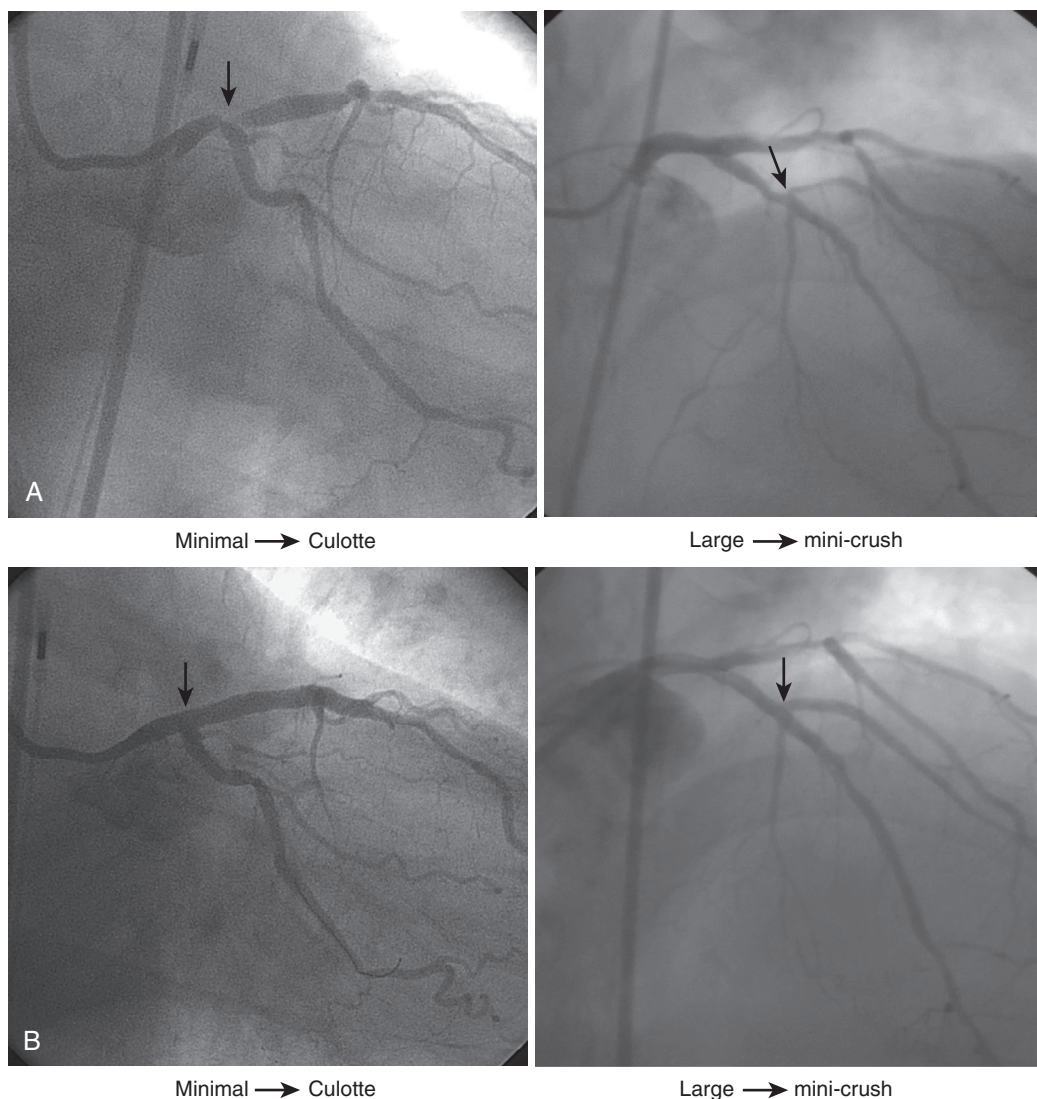


FIGURE 10.17 Angiography demonstrating a left main coronary artery bifurcation with minimal discrepancy between distal left main and circumflex (A, and Video 10.5) that would be suitable for culotte stenting (B, left panel and Video 10.6) compared with a left anterior descending coronary artery (LAD) diagonal bifurcation with a large discrepancy between the LAD and diagonal (A, right panel and Video 10.7) that would not be suitable for culotte stenting but should rather be treated with a mini-crush technique (B, right panel and Video 10.8). MB, Main branch; SB, side branch.

Double-Stenting Technique Description

This section describes how to perform and select patients for all the currently used techniques for elective double stenting. We again stress that it is not only the specific technique but rather meticulous attention to performing the procedure that is important in ensuring success and improving long-term results.

The Culotte Technique

The culotte technique provides near-perfect coverage of the carina and SB ostium at the expense of an excess of metal covering the proximal end.⁷⁹ It gives the best immediate angiographic result, and theoretically, it may guarantee a more homogeneous distribution of struts and drug at the site of the bifurcation. This technique can be used in almost all true bifurcation lesions irrespective of the bifurcation angle. The only anatomic limitation to the culotte technique is when there is a large mismatch between the proximal MB

and SB diameters because of the risk of incomplete SB stent apposition to the proximal MB. The main disadvantage of the technique is its complexity is rewiring of both branches through the stent struts, which can be technically demanding and time consuming and thus we do not suggest this technique if both branches are dissected after predilation.

This technique can be performed with a 6-Fr guiding catheter (Figure 10.22). The steps are as follows:

1. Both branches are wired and predilated.
2. A stent is deployed across the most angulated branch, usually the SB, with only a few millimeters of protrusion into the PMV (mini-culotte).
3. A POT is performed to fully appose the SB stent struts in the PMV before wire recrossing.
4. The nonstented branch is rewired through the stent struts and dilated.
5. A second stent is advanced and expanded into the non-stented branch, usually the MB.

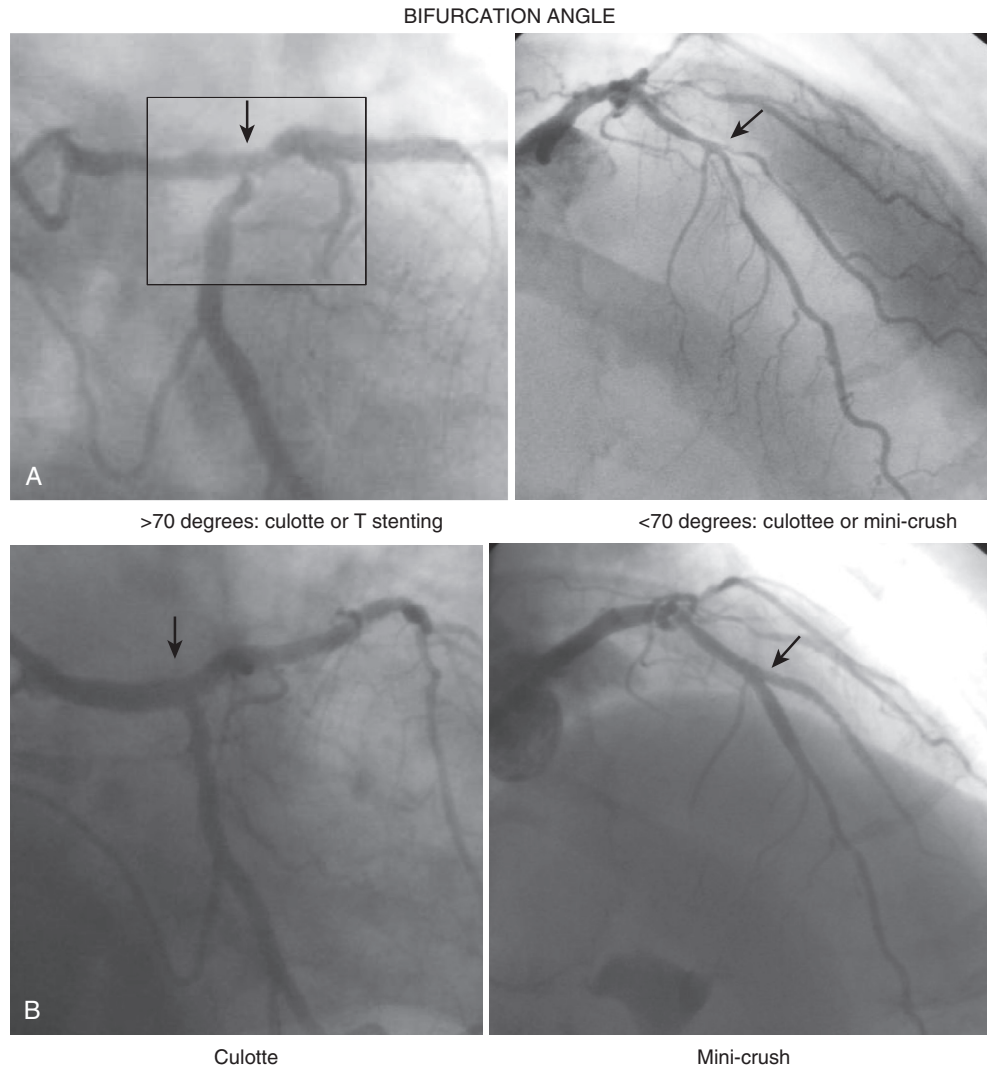


FIGURE 10.18 Angiography demonstrating a left main coronary artery bifurcation with an angle between the distal left anterior descending coronary artery (LAD) and circumflex greater than 70 degrees (**A**, left panel and [Video 10.9](#)) in which culotte or T stenting would be preferred over the crush (**B**, left panel and [Video 10.10](#)) compared with a LAD diagonal bifurcation with an angle less than 70 degrees between the distal LAD and diagonal (**A**, right panel and [Video 10.11](#)) that would not be suitable for T stenting but should rather be treated with a mini-crush or culotte technique (**B**, right panel and [Video 10.12](#)). MB, Main branch; SB, side branch.

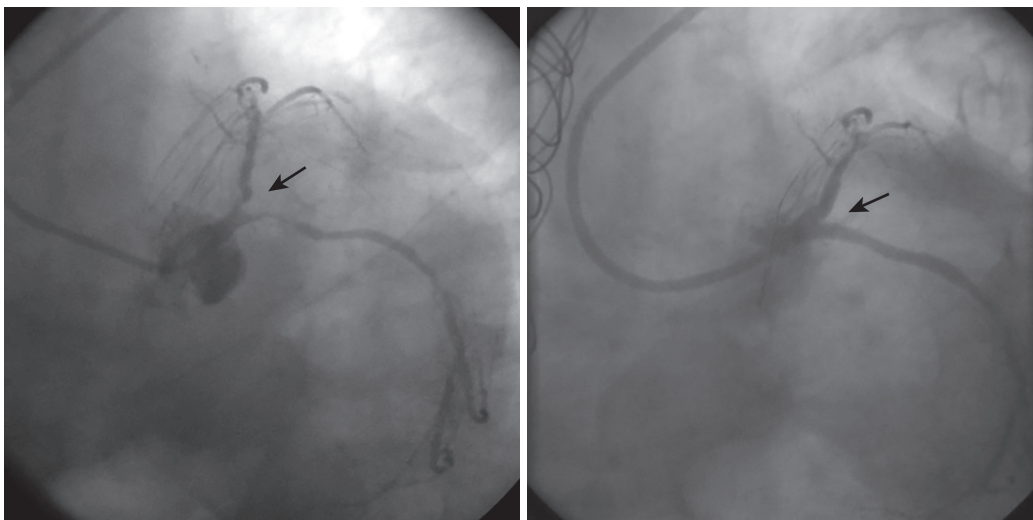


FIGURE 10.19 **A** and **B**, Angiography images showing a Medina 0.1.1 bifurcation (arrows) with minimal disease in the proximal main branch (left panel) that would be suitable for V stenting (right panel, see Videos 10.13 and 10.14).

DISSECTION OF MB AND SB

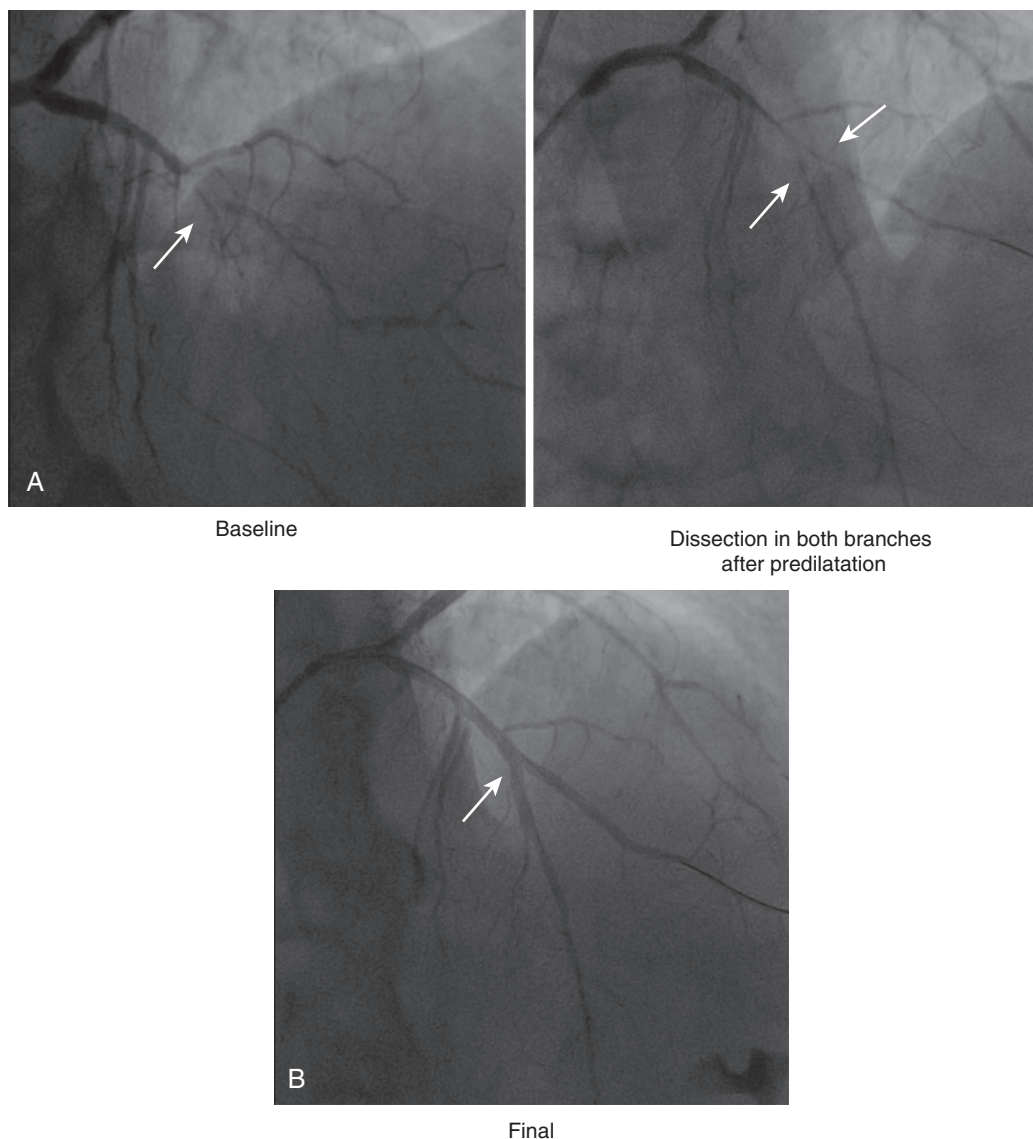


FIGURE 10.20 Angiography showing a chronic total occlusion (arrows) of a left anterior descending coronary artery (LAD) diagonal bifurcation (**A**, left panel and [Video 10.15](#)) that after wire passage and predilatation shows a dissection of both branches (**A**, right panel and [Video 10.16](#)). The bifurcation was treated with the double kissing mini-crush technique because it guarantees patency of both branches and avoids having to recross stent struts into a dissected branch (**B** and [Video 10.17](#)). MB, Main branch; SB, side branch.

6. A POT is performed again to ensure full apposition of the MB stent before wire recrossing into the SB and the balloon inflation toward the SB.
7. Finally, kissing balloon inflation is performed. When performing the kissing inflation, we prefer using non-compliant balloons and dilating each limb of the culotte at high pressure (≥ 16 atm) individually before simultaneously inflating both balloons at 8 to 12 atm.

Although the culotte technique may be technically more challenging than other techniques, a number of factors can facilitate its successful performance. When rewiring the other branch after stent placement, we always first place the guidewire distal into the stented branch to be sure that we have not passed under the stent struts before recrossing into the branch. In performing the culotte technique, we recommend stenting the branch with the sharpest angle first. This has the advantage that recrossing stent struts

into the less angulated branch will be easier as will passing the second stent through stent struts into a less angulated branch. However, this conventional practice has recently been challenged in the Nordic Stent Technique Study, in which the authors recommended stenting of the MB first to avoid acute closure of the MB.⁸² This approach guarantees patency of the MB and may avoid one of the potential problems of performing the culotte technique in which we always need to remove the wire from one of the two branches, and patency of this branch is not guaranteed. For this reason, we prefer not to perform the culotte technique if there is a dissection in both branches after predilatation.

The Mini-Crush Technique (Side Branch Stent Crushed by the Main Branch Stent)

The main advantage of the crush technique is that immediate patency of both branches is assured; therefore, it

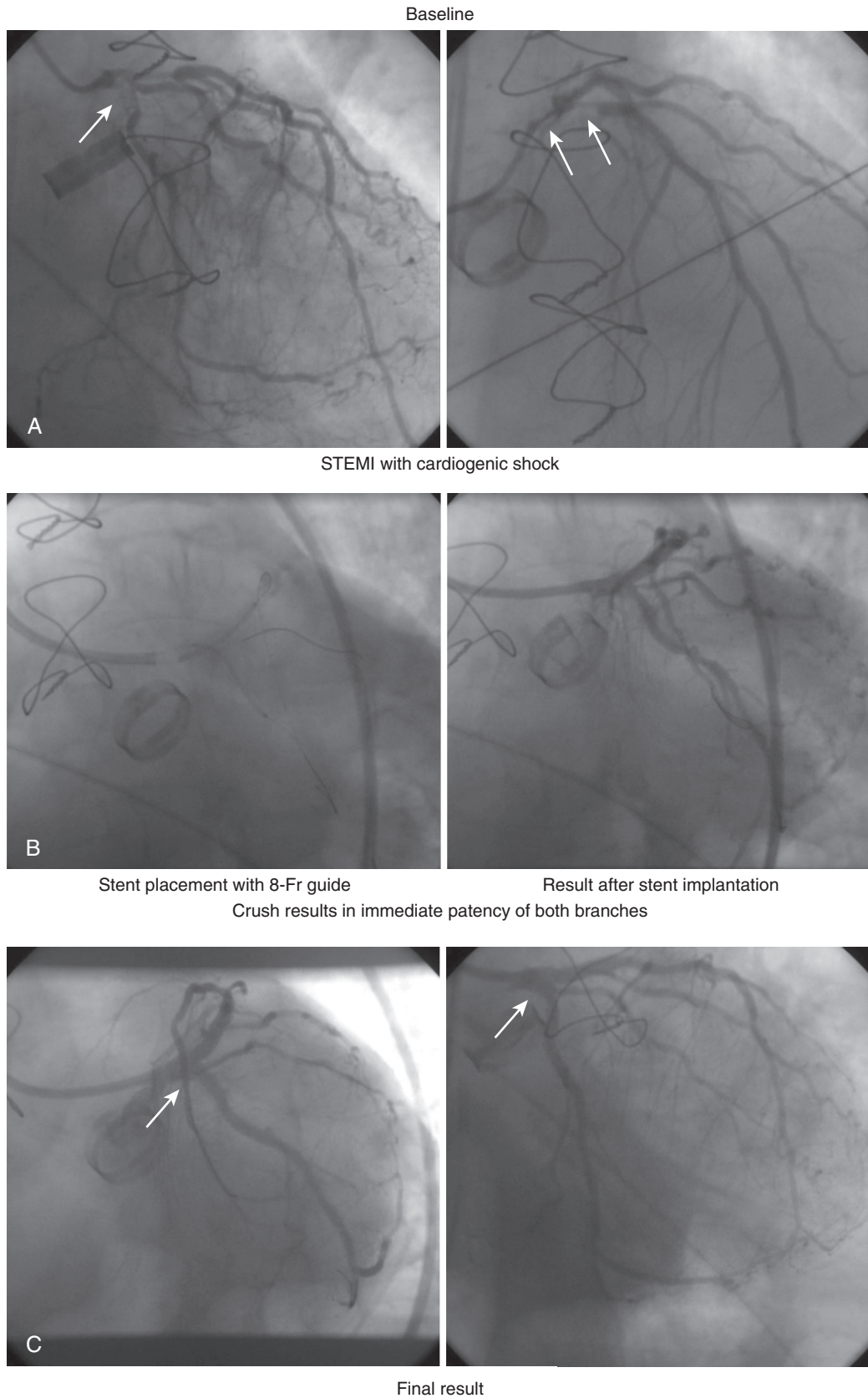


FIGURE 10.21 Baseline angiography in a patient presenting with ST-segment elevation myocardial infarction (STEMI) and cardiogenic shock showing severe thrombotic occlusion of the distal left main (arrows) involving the proximal left anterior descending coronary artery and circumflex (A and Videos 10.18 and 10.19). In this emergency situation in which rapid and immediate patency of both branches needs to be guaranteed, the V-stenting and classical mini-crush techniques are preferred. The procedure was performed with an 8-Fr guiding catheter. Both stents were placed at the same time with the side branch (SB) stent protruding minimally into the main branch (MB) (B, left panel and Video 10.20). The SB stent was inflated first, and stent delivery balloon was removed followed by inflation of the MB stent. Angiography immediately after stent implantation confirmed patency of both branches (B, right panel and Video 10.21), and the final result after optimization with a two-step final kissing balloon inflation is shown in C and Video 10.22 and Video 10.23.

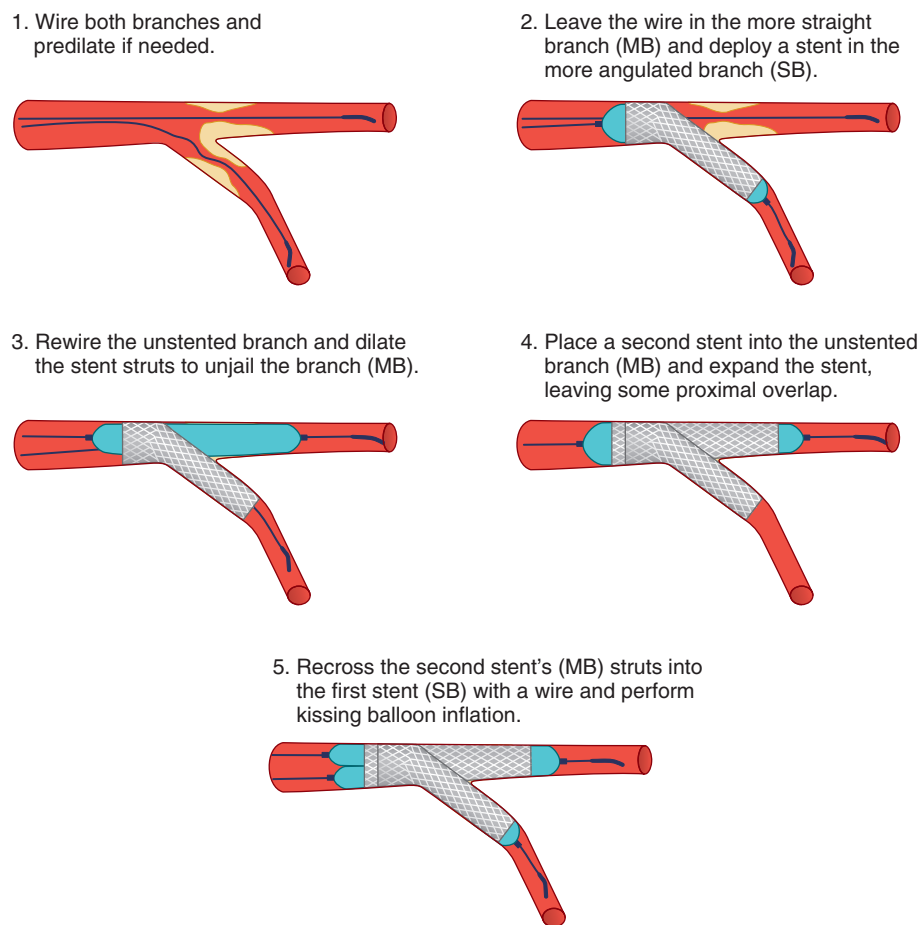


FIGURE 10.22 A schematic representation of the culotte technique. MB, Main branch; SB, side branch.

should be applied in conditions of instability or when the anatomy appears complex.²⁴ This objective is notably important when the SB is functionally relevant or difficult to wire. In addition, this technique provides excellent coverage of the ostium of the SB. This technique can be used in almost all true bifurcation lesions but should be avoided in wide-angle bifurcations. The main disadvantage is that to perform FKBI, there is the need to recross multiple struts with a wire and a balloon. However, only the SB has to be rewired and not both branches as in the culotte technique. The crush technique has evolved and is nowadays performed with less stent protrusion into the MB (i.e., mini-crush) and mandatory two-step FKBI.^{83,84}

The technique requires at least a 7-Fr guiding catheter (Figure 10.23). The steps are as follows:

1. Both branches are wired and fully dilated.
2. The SB stent is positioned in the SB and then the MB stent is advanced.
3. The SB stent is pulled back into the MB about 1 to 2 mm and is verified in at least two projections.
4. The SB stent is deployed at least at 12 atm. The balloon is deflated and removed from the guiding catheter. An angiogram is taken to verify that the SB has an appropriate lumen and normal flow and that no distal dissection or residual lesions is present. If an additional stent is needed in the SB, this is the time to implant it. After this check, the stent in the MB is fully deployed at high pressure, usually above 12 atm. An angiogram is taken after removal of the balloon from the MB. When we use this

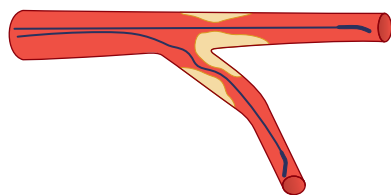
technique, we keep only a single deflator on the table that is connected to the SB stent. This prevents inadvertent deployment of the MB stent first, thereby crushing the undeployed SB stent.

5. The SB is rewired. It is important to perform a two-step FKBI. First, we suggest a dilation of the stent toward the SB with a balloon appropriately sized to the diameter of this branch and inflated at high pressure (≥ 16 atm) and then FKBI with a second balloon in the MB with an inflation pressure about 8 to 14 atm in both balloons.

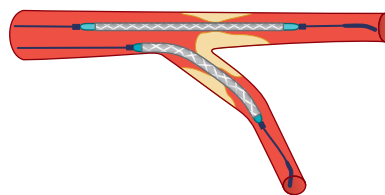
Double-Kissing Mini-Crush

When there is the need to perform the mini-crush technique and a 6-Fr guiding catheter is the only available approach (radial approach), the “step crush” or “the modified balloon crush” technique can be used. The final result is basically similar to that obtained with the standard crush technique, with the only difference that each stent is advanced and deployed separately. We now routinely perform the DK crush technique. This technique is a modification of the step crush in which kissing balloon inflation is performed twice: first after the SB stent is crushed by the MB balloon and then the routine FKBI at the end of the procedure. DK crush may result in less stent distortion and improved stent apposition and may facilitate FKBI. This technique may be superior to the classic crush technique in optimizing acute procedural results and possibly also improves clinical outcomes by facilitating FKBI in all patients.⁸⁵ Unless there is a compelling reason to obtain immediate patency of the MB

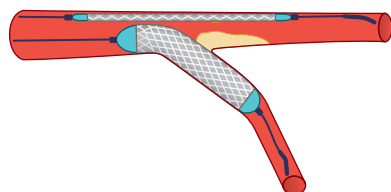
1. Wire both branches and predilate if needed.



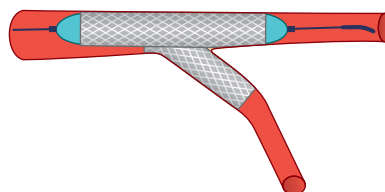
2. Advance the two stents. The MB stent is positioned proximally. The SB stent will protrude only minimally into the MB.



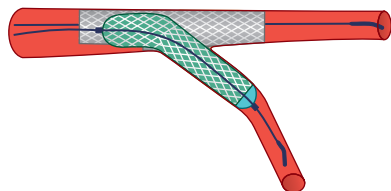
3. Deploy the SB stent.



4. Check for optimal result in the SB and then remove the balloon and wire from the SB. Deploy the MB stent.



5. Rewire the SB and perform high-pressure dilation.



6. Perform final kissing balloon inflation.

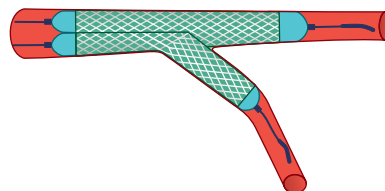


FIGURE 10.23 A schematic representation of the classical mini-crush technique. *MB*, Main branch; *SB*, side branch.

and the SB (need for the standard mini-crush technique with a 7- or 8-Fr guiding catheter), we recommend that the DK crush technique should be the default two-stent technique when this approach is selected as intention to treat.

This technique can be performed with a 6-Fr guiding catheter (Figure 10.24). The steps are as follows:

1. Both branches are wired and fully dilated
2. The stent is advanced in the SB, protruding a few millimeters into the MB. A balloon is advanced in the MB over the bifurcation.
3. The stent in SB is deployed, balloon is pulled back slightly into the PMV, and a second inflation is performed at higher pressure before removing the balloon. An angiogram is performed, and if the result is adequate, the wire is also removed.
4. The MB balloon (sized 1:1 with the PMV) is then inflated at high pressure (to crush the protruding SB stent) and removed.
5. The crushed SB stent is then recrossed proximally because crushing may result in malapposition at the distal SB ostium wall, and inadvertent wiring of this space will result in incomplete SB coverage.
6. A two-step kissing balloon inflation is performed.
7. A second stent is advanced in the MB and deployed (usually at ≥ 12 atm).
8. The next steps are similar to those of the classical crush technique and involve recrossing into the SB, SB stent dilation, and two-step FKBI.

An important change in the classical crush technique is that we now try to limit the area of crush stenting and multiple layering of stent struts by performing a mini-crush. The mini-crush may be associated with more complete endothelialization (and theoretically less stent thrombosis) and easier recrossing of the crushed stent. Finally, the bifurcation angle may be an important factor to consider when performing the crush technique. When the angle between the MB and SB is closed to 90 degrees, it is possible to minimize the gap even without crushing the SB stent and using the modified T technique. Furthermore, a bifurcation angle B of 50 degrees or greater between the two branches has been suggested as an independent predictor of MACE after crush stenting.⁸⁶

T and Modified T Techniques

The T technique is the most frequently used to crossover from provisional stenting to stenting the SB and is most suited to bifurcations when the angle between the branches is close to 90 degrees. This technique is less laborious than the crush or culotte technique. In our view, the T technique is associated with the risk to leave a small gap between the stent implanted in the MB and the one implanted in the SB. This gap may be a factor contributing to an uneven distribution of the drug, hence leading to ostial restenosis at the SB. For this reason, this technique has largely been replaced by the modified T-stenting technique. Currently, we rarely perform the classical T technique in our practice,

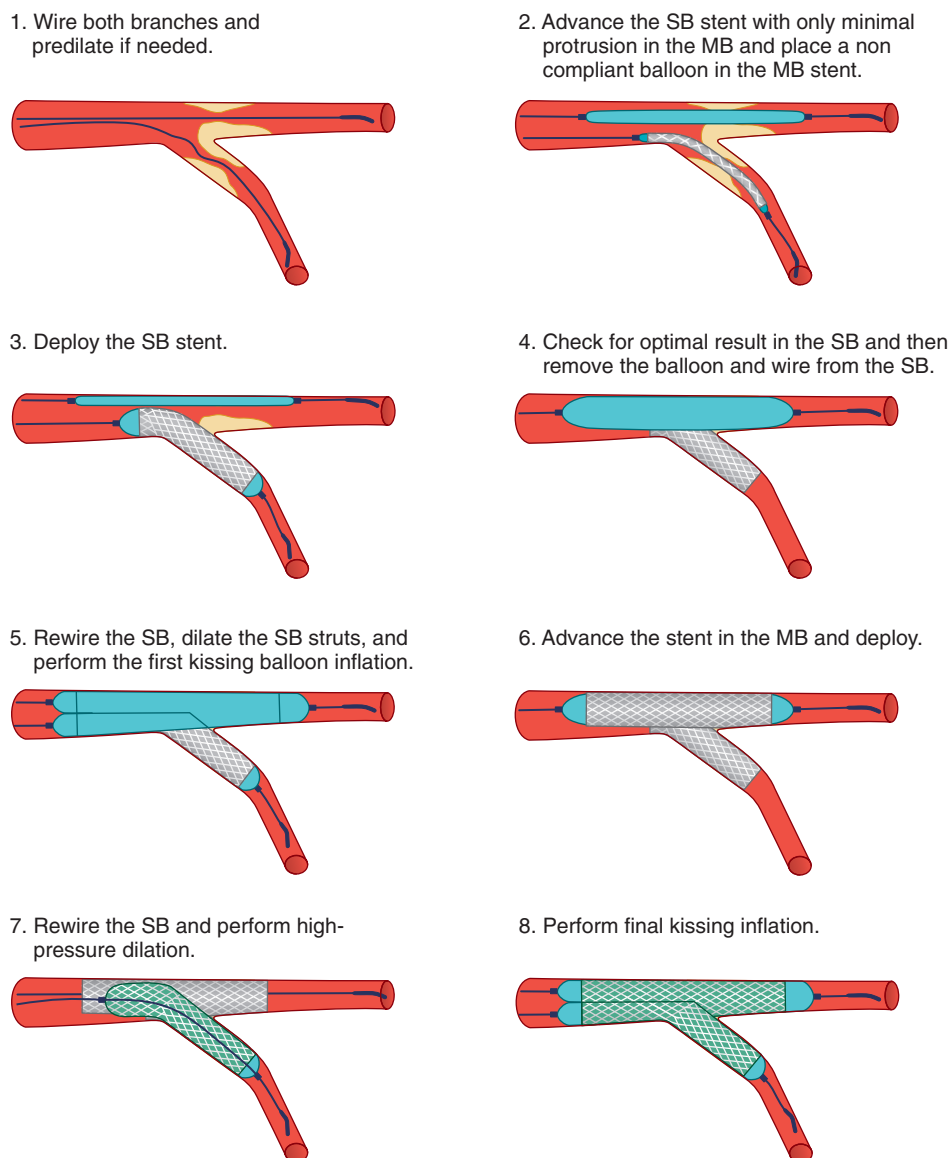


FIGURE 10.24 A schematic representation of the double-kissing mini-crush technique. *MB*, Main branch; *SB*, side branch.

and in our opinion, there are two reasons to perform the classical T technique: (1) to place a stent at the ostium of an SB after placement of a stent in the MB because the result at the SB ostium was unsatisfactory (provisional SB stenting; in this situation, we have replaced the classical T technique with the TAP), and (2) to perform stenting at the ostium of the SB when there is isolated SB ostial stenosis (e.g., T-balloon stenting).

The classical T technique requires a 6-Fr guiding catheter. The steps are as follows:

1. Position a stent first at the ostium of the SB, being careful to avoid stent protrusion into the MB while at the same time trying to minimize any possible gap.
2. Deploy the stent and remove the balloon from the SB (keep the wire in the SB).
3. Advance and deploy the MB stent.
4. Rewire SB and then remove the jailed wire.
5. Perform SB balloon dilation and FKI.

This description of T stenting describes the situation in which the operator decides to stent the SB first. However,

in majority of cases, the T-stenting technique is performed after MB and provisional SB stenting for a suboptimal result of flow-limiting dissection.

MODIFIED T TECHNIQUE. Modified T stenting is a variation performed by simultaneously positioning stents at the SB and MB (requires at least a 7-Fr guiding catheter) with the SB stent minimally protruding into the MB, when the angle between the branches is close to 90 degrees (Figure 10.25). The SB stent is deployed first, and then after wire and balloon removal from the SB, the MB stent is deployed. The procedure is completed with FKBI.

THE V AND THE SIMULTANEOUS KISSING STENT TECHNIQUES. The V and the simultaneous kissing stent (SKS) techniques are performed by delivering and implanting two stents together.^{87,88} One stent is advanced into the SB and the other into the MB. Both stents are pulled back to create a Neocarina as close as possible to the original one. When the two stents protrude into the MB with the creation of a double barrel and a very proximal carina, the technique is called SKS.⁸⁸ The main advantage of these

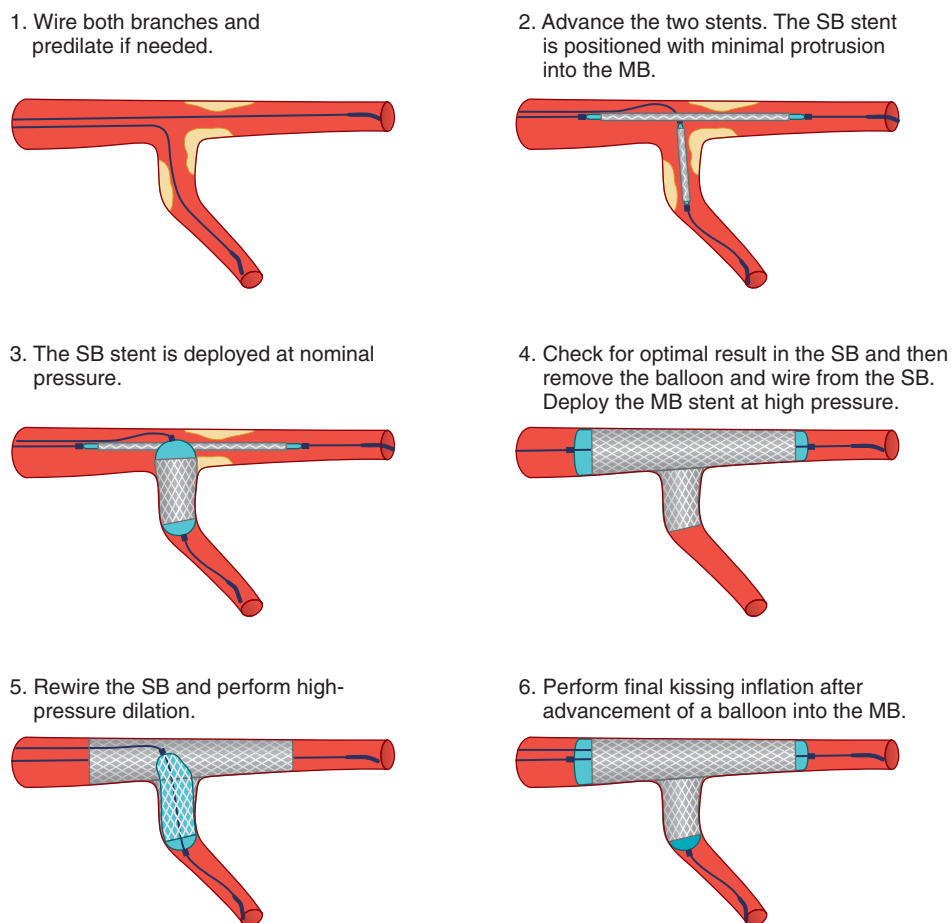


FIGURE 10.25 A schematic representation of the modified T-stenting technique. *MB*, Main branch; *SB*, side branch.

techniques is that access to both branches is always preserved during the procedure with no need for rewiring any of the branches. V stenting is relatively easy and fast and thus ideal in emergencies. In addition, when FKI is performed, there is no need to recross the SB stent. V stenting is ideal for Medina 0:1:1 bifurcations with large proximal MBs that are relatively free from disease and with a less than 90-degree angle between both branches. We reserve this technique for patients with a short LMCA free from disease and critical disease of both the LAD and LCX ostia. Interestingly, a modified V technique (Y or skirt technique) with two stents deployed together on the SB and distal MB and a stent (manually crimped onto two balloons) placed in the proximal MB was the first double-stenting technique used for coronary bifurcations and to be demonstrated in a live case course.⁸⁹

This technique requires at least a 7-Fr guiding catheter (Figure 10.26). The steps are as follows:

1. Both branches are wired and fully predilated.
2. Two stents are positioned into the branches with a slight protrusion of both stents into the proximal MB. Different operators allow a variable amount of protrusion, creating sometimes a rather long (≥ 5 mm) double barrel in the proximal MB (SKS). Although we recognize that it is impossible to be so accurate in positioning the stents exactly at the ostium of each branch, we generally try to limit the length of the new carina to less than 5 mm. Sometimes it is necessary to advance the first

stent more distally into the vessel to facilitate the advancement of the second stent. This maneuver is essential when the kissing stent technique is used to stent a trifurcation using three kissing stents (need of a 9-Fr guiding catheter). After accurate stent positioning, it is important to verify their correct placement in two projections before deploying the stents.

3. Each stent is deployed individually at high pressure of 12 atm or more. Some operators prefer deploying the stents simultaneously. When the stents are deployed simultaneously, the operator needs to be aware of the risk of proximal MB dissection. This can be avoided by using a lower deployment pressure.
4. High-pressure sequential single-stent postdilation is performed followed by medium-pressure FKI with short and noncompliant balloons. Balloon sizes are chosen according to the diameter of the treated vessels. In the event that the reference vessel size proximal to the bifurcation is relatively small, FKBI should be performed using low-pressure inflation to avoid proximal dissection.

There are several limitations for this technique that need to be considered: (1) the possibility of balloon barotrauma to the proximal MB during stent deployment or postdilation, which can lead to dissection, progression of disease, or proximal edge restenosis; (2) if a proximal stent becomes necessary to treat a proximal dissection, there is almost always the risk of leaving a small gap, and the stent needs to be directed toward one

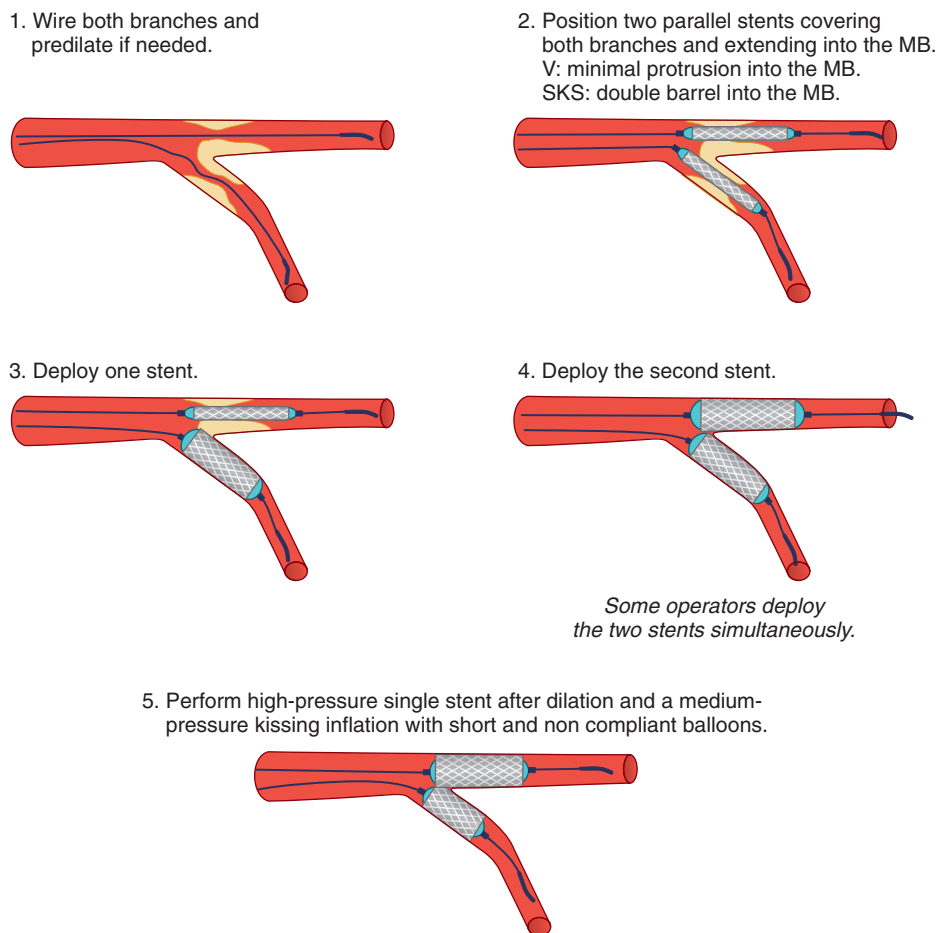


FIGURE 10.26 A schematic representation of the V-stenting technique. MB, Main branch; SKS, simultaneous kissing stent.

of the two arms of the V; (3) if restenosis occurs in the neocarina or at the proximal stent edge, it would require converting to the crush technique for treatment, which would make recrossing into the branch covered by the crushed stent potentially challenging because four layers of stent struts will need to be traversed; and (4) if disease distal to the V stenting or SKS site needs to be treated at follow-up, rewiring the stented vessels may be complicated by wire passage behind stent struts. If additional guidewires need to be inserted during the procedure to treat distal disease, we recommend using a dual-lumen microcatheter such as the Twin-Pass catheter (Teleflex) or Sasuke (Asahi). When previous V stenting or SKS needs traversing at another PCI, we suggest passing through the stent with a loop on the radiopaque part of the guidewire to prevent the guidewire from passing through stent struts and confirming the wire position with intravascular imaging.

The SKS technique results in a new metallic carina quite proximally into the LMCA. We do not know at present what the long-term outcome risks are of leaving this exposed double stent layer in a vessel when using DESs. There have been case reports describing a thin diaphragmatic membranous structure at the new carina (at the level of the kissing struts), resulting in an angiographic filling defect. Other than producing a very distressing angiographic appearance, the exact long-term significance

and relation to adverse advents of this membrane is not known.⁸¹

Final Kissing Inflation After Double Stenting

Final kissing balloon inflation for carina reconstruction is mandatory in two-stent techniques. A special mention needs to be made of the importance of FKI when implanting two stents in LMCA bifurcations. FKI is not only important to correct stent distortion and expansion^{38,39} but is especially important to fully expand the stent in the distal LMCA, where the diameter is usually much larger than the diameters of the LAD and LCX. The effective balloon diameter in the distal LMCA (which we calculate as the MB balloon diameter plus one-third of the SB balloon diameter) from the two balloons used for FKBI is essential to fully expand the stent(s). In performing FKBI, it is critical to choose noncompliant postdilation balloons of appropriate size; that is, the kissing balloons should be the same size or larger than the deploying balloons to prevent stent distortion.³⁸ As previously mentioned, individual noncompliant high-pressure “ostial” postinflations are mandatory in complex stenting techniques to achieve full stent expansion. When performing FKBI, we inflate both balloons simultaneously and slowly, which makes “melon seeding” less likely. We also deflate the balloons simultaneously to avoid distortion. High-pressure proximal stent inflation using a short noncompliant balloon should be

considered for correction of possible proximal stent distortion after FKBI.

Difficult Access to the Side Branch or Main Branch After Stenting

Access to the SB is one of the greatest challenges in bifurcation PCI. Difficult access to the SB or MB can occur either at the start of the procedure or after SB or MB stenting. Difficulty may occur in recrossing the stent struts with a guidewire or advancing a balloon through the stent struts. We would like to address the problem of rewiring and advancing balloons into one of the branches after having stented the other branch (MB or SB), which is often the greatest difficulty with double-stenting techniques such as the mini-crush or even culotte. In our experience, recrossing into the SB through the MB stent struts or vice versa is usually possible using the Rinato-Prowater or Sion Blue/Black wires. In difficult situations, we have also successfully used the Pilot 50 and 150 (Abbott Vascular Devices), Fielder FC, Asahi Intermediate, Miracle, or Ultimate 3/4.5 gm (Asahi Intecc Co) wires. However, we are very cautious about using hydrophilic guidewires when recrossing into the SB because of the risk of wire-induced dissection and perforation. If SB rewiring fails despite using different wire curves and wires, a possible cause may be the presence of underexpanded stents in the MB, impeding wiring of the ostium. Proximal MB stent postdilation with the POT may be useful in correcting the underexpansion and causing protrusion of MB struts into the SB, even with double-stenting techniques. The jailed wire in the branch should always be left in place as a marker until complete recrossing has been done. After having recrossed into the branch with a guidewire, there may subsequently be great difficulty advancing a balloon through the struts to dilate them. We frequently try first to cross through the stent struts with the smallest balloon we have on the table. If this balloon fails, we then use a 1.25- or 1.5-mm-diameter balloon to separate struts and allow a larger balloon to pass. If the 1.5-mm balloon cannot cross, we consider recrossing with a second wire while the first wire remains in place to traverse the stent struts in another spot. If balloon insertion through the strut still proves impossible, the stent should be further dilated. Another attempt should be made with a 1.5-mm coaxial balloon. Another trick that sometimes works is to advance the balloon as close as is possible to the stent struts, inflating the balloon to at least 12 to 14 atm for 20 seconds and while deflating the balloon to attempt advancing it farther. Repeating this maneuver can often result in the balloon slowly advancing through the stent struts.^{11,81} If it still proves impossible to recross into the branch, another technique we have used is to try to pass a 1.5-mm balloon over the jailed wire behind the stent struts to either (1) redilate a subtotally occluded or dissected branch ostium and then try again to pass the stent struts with a guidewire or (2) to convert the procedure into a reverse crush.

Ancillary Devices and Procedures

Intracoronary Imaging

Intravascular ultrasound provides valuable baseline information regarding plaque distribution, especially in relation

to the SB ostium, plaque composition, vessel size, and the severity of angiographically ambiguous LM lesions. An example is the study by Furukawa et al.³¹ that demonstrated that the presence and severity of ostial SB plaque as observed by IVUS is the most important predictor of SB occlusion after bifurcation PCI. IVUS after stent implantation is essential for correct stent optimization, especially in complex bifurcations, LM lesions, or when 2S techniques are applied by evaluating stent expansion and apposition, especially of the SB ostium; proximal or distal dissection; and periadventitial hematoma. Costa et al.⁹⁰ demonstrated the importance of IVUS when performing complex techniques such as the crush because incomplete crushing (i.e., incomplete apposition of the three layers of main and SB stent struts) and ostial SB stent underexpansion is common and often not suspected angiographically. However, the most important unanswered question that still remains is whether routine IVUS use results in improved clinical outcomes. Specifically regarding bifurcations, Kim et al.⁹¹ performed a retrospective evaluation of 758 patients with de novo non-LM coronary bifurcation lesions. In patients receiving DESs, IVUS-guided stenting significantly reduced the 4-year long-term mortality rate (HR, 0.24; 95% CI 0.06–0.86; $P = .03$) and late stent thrombosis (0.4% vs 2.8%; $P = 0.03$, log-rank test) compared with angiographically guided stenting. A Korean multicenter bifurcation registry evaluated 487 propensity-matched pairs and found a significantly lower rate of death or MI in the IVUS-guided group than the angiography-guided group (3.8% vs 7.8%; $P = .04$).⁹² Chen et al.⁹³ evaluated outcomes of IVUS-guided systematic two-stent techniques and found a significantly lower rate of late stent thrombosis at 12-month follow-up (0% in the IVUS-guided group vs 4.9% in the angiography-guided group; $P = .029$). Finally, the 5-year results from DKCRUSH-II also suggested a reduced rate of MI in patients who underwent IVUS assessment (1.8% vs 5.4%; $P = .043$).⁹⁴

Similarly, in LM lesions, IVUS guidance was associated with a tendency to a lower risk of 3-year mortality rate compared with angiography-guidance (6.0% vs 13.6%; log-rank $P = .063$; HR, = 0.54; 95% CI, 0.28–1.03; $P = .061$), in the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization) registry.⁹⁵ IVUS guidance, however, did not modify the risk of MI or repeat revascularization. Similarly, in our multicenter registry evaluating 731 LMCA lesions (76.5% involving the distal LM) undergoing DES implantation, IVUS guidance was associated with reduced cardiac death (OR, 0.93; 95% CI, 0.16–0.93; $P = 0.03$) at univariate exact logistic (unconditional) analysis.⁹⁶ de la Torre Hernandez et al.⁹⁷ evaluated the clinical impact of IVUS guidance on DES implantation for unprotected LM disease based on patient-level pooled analysis of four registries. Survival free rates of cardiac death, MI, and TLR at 3 years were 88.7% in the IVUS group and 83.6% in the no-IVUS group ($P = .04$) for the overall population; 90% and 80.7%, respectively ($P = .03$), for the subgroup with distal LM lesions; and 83.3% and 59%, respectively ($P = .02$), for the distal LM subgroup treated with two stents.

Although there have not been any published randomized trials evaluating imaging guidance in bifurcations, a

3-year follow-up of the Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions (ULTIMATE) trial showed a significant reduction of target vessel failure with IVUS in the bifurcation subgroup (HR, 0.48; 95% CI, 0.27–0.87).⁹⁸

Optical coherence tomography may have better resolution for evaluation of plaque characteristics, stent expansion, apposition, in-stent tissue protrusion, vessel dissection, guidewire recrossing position, and stent deformation. However, it is limited by reduced imaging depth, increased contrast usage, and difficulty assessing the LM ostium.

Despite the lack of randomized data, the authors strongly believe that intracoronary imaging guidance using modern and feasible criteria should be used when implanting stents in bifurcation lesions involving a large amount of myocardium at jeopardy or when complex double stenting is performed.

Lesion Preparation: Role of Debulking

Although lesion preparation should not be considered routine, it should be used when (1) there are diffuse and severe calcifications, (2) the predilating balloon does not cross the lesion or fully expand, (3) it is difficult to cross the lesion with the stent. In these cases, we usually perform rotational atherectomy with a 1.25- or 1.5-mm burr. However, if the IVUS catheter crosses the lesion, we use information on the plaque morphology to determine our lesion debulking strategy in the following way: (1) superficial calcium extending more than 180 degrees may demand lesion preparation with rotational atherectomy (Rotablator, Boston Scientific) or with orbital atherectomy (CSD); (2) severe fibrosis or moderate calcifications may demand a cutting balloon (cutting balloon Ultra and Flextome, Boston Scientific), scoring balloons (AngioSculpt, Angioscore), or noncompliant balloons sized to the media to media diameter; and (3) the presence of soft plaque may permit direct stenting. We generally prefer scoring balloons to cutting balloons because they have a better profile and tend to cause less vessel dissections and perforations. We undersize the scoring balloon by 0.5 to 0.75 mm less than the reference vessel diameter obtained by IVUS and perform high-pressure inflations greater than 14 atm (usually 18–20 atm). Intravascular lithotripsy has also become an important tool in treating calcified bifurcations, including LM, because of safety an advancement over standard wires. Also, they can be performed with both branch wires in place and may have a synergistic effect with atherectomy.⁹⁹

Drug-Coated Balloons in Bifurcations

Drug-coated balloons (DCBs) may potentially have a role in bifurcations as part of a provisional strategy of a DCB on the SB and a DES on the MB to avoid double stenting in bifurcations with large SBs. Theoretical advantages of this strategy are a reduction of SB restenosis by homogenous drug delivery; preservation of normal bifurcation anatomy; and the avoidance of excess metal overlap, distortion, malapposition, and underexpansion in the bifurcation. This strategy may be particularly interesting for left circumflex ostium where the results with DESs continue to be disappointing. A meta-analysis of 10 studies (934 patients), including 5 RCTs and 5 nonrandomized observational

studies, showed that DCB was associated with significantly lower MACE rates at 9-month (OR, 0.21; 95% CI, 0.05–0.84; $P = .03$) and 12-month follow-up (OR, 0.45; 95% CI, 0.22–0.90; $P = .02$).¹⁰⁰ These results were consistent with A drug-eluting Balloon for the trEatment of coronary bifurcatiON lesions in the side branch: a prospective multicenter randomized (BEYOND) clinical trial in China that randomized 222 patients treated with a provisional approach for non-LM bifurcation lesions to SB dilation with a paclitaxel DCB versus regular balloon angioplasty. SB diameter stenosis was less at 9 months in the DCB cohort (29% vs 40%; $P < .0001$), but clinical outcomes were unchanged.¹⁰¹ However, we expect to see many more RCTs over the next few years to evaluate both sirolimus and paclitaxel DCBs to reduce SB restenosis as part of the provisional approach and to avoid SB stenting when two-stent techniques are required. Finally, when evaluating the effectiveness of DEBs, it should be remembered that there is no class effect with DEBs and that different DEBs vary considerably regarding efficacy.

CONCLUSIONS

The introduction of second-generation DESs and refinement in the stenting techniques made a remarkable improvement in the treatment of bifurcation lesions. The current appropriate application of provisional stenting and perfecting stent techniques when implanting two stents are improving the acute results and long-term follow-up. Particular attention should be given to dual antiplatelet therapy when treating these lesions, especially when two stents have been implanted.

SELECTED REFERENCES

Visit Elsevier eBooks+ to access the complete list of references.

- Lefevre T, Louvard Y, Morice MC, et al. Stenting of bifurcation lesions: classification, treatments, and results. *Catheter Cardiovasc Interv*. 2000;49:274-283.
- Louvard Y, Lefevre T, Morice MC. Percutaneous coronary intervention for bifurcation coronary disease. *Heart*. 2004;90:713-722.
- Medina A, Suarez de Lezo J, Pan M. A new classification of coronary bifurcation lesions. *Rev Esp Cardiol*. 2006;59:183.
- Latib A, Colombo A. Bifurcation disease: what do we know, what should we do? *J Am Coll Cardiol Interv*. 2008;1:218-226.
- Hahn JY, Chun WJ, Kim JH, et al. Predictors and outcomes of side branch occlusion after main vessel stenting in coronary bifurcation lesions: results from the COBIS II Registry (Coronary Bifurcation Stenting). *J Am Coll Cardiol*. 2013;62:1654-1659.
- Yamashita T, Nishida T, Adamian MG, et al. Bifurcation lesions: two stents versus one stent—immediate and follow-up results. *J Am Coll Cardiol*. 2000;35:1145-1151.
- Thuesen L, Kelbaek H, Klovgaard L, et al. Comparison of sirolimus-eluting and bare metal stents in coronary bifurcation lesions: subgroup analysis of the Stenting Coronary Arteries in Non-Stress/Benestent Disease Trial (SCANDSTENT). *Am Heart J*. 2006;152:1140-1145.
- Windecker S, Latib A, Kedhi E, et al. Polymer-based versus polymer-free stents in high bleeding risk patients: final 2-year results from Onyx ONE. *JACC Cardiovasc Interv*. 2022;15:1153-1163.
- Colombo A, Moses JW, Morice MC, et al. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation*. 2004;109:1244-1249.
- Pan M, de Lezo JS, Medina A, et al. Rapamycin-eluting stents for the treatment of bifurcated coronary lesions: a randomized comparison of a simple versus complex strategy. *Am Heart J*. 2004;148:857-864.
- Steigen TK, Maeng M, Wiseth R, et al. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation*. 2006;114:1955-1961.
- Ferenc M, Gick M, Kienle RP, et al. Randomized trial on routine vs. provisional T-stenting in the treatment of de novo coronary bifurcation lesions. *Eur Heart J*. 2008;29:2859-2867.
- Colombo A, Bramucci E, Sacca S, et al. Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurca-

- tions: the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) Study. *Circulation*. 2009;119:71-78.
25. Hildick-Smith D, de Belder AJ, Cooter N, et al. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation*. 2010;121:1235-1243.
 26. Chen SL, Santoso T, Zhang JJ, et al. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions: results from the DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) trial. *J Am Coll Cardiol*. 2011;57:914-920.
 27. Kumsars I, Holm NR, Niemela M, et al. Randomised comparison of provisional side branch stenting versus a two-stent strategy for treatment of true coronary bifurcation lesions involving a large side branch: the Nordic-Baltic Bifurcation Study IV. *Open Heart*. 2020;7:e000947.
 28. Hildick-Smith D, Behan MW, Lassen JF, et al. The EBC TWO Study (European Bifurcation Coronary TWO): a randomized comparison of provisional T-stenting versus a systematic 2 stent culotte strategy in large caliber true bifurcations. *Circ Cardiovasc Interv*. 2016;9(9):e003643.
 33. Naganuma T, Latib A, Basavarajiah S, et al. The long-term clinical outcome of T-stenting and small protrusion technique for coronary bifurcation lesions. *JACC Cardiovasc Interv*. 2013;6:554-561.
 35. Koo BK, Kang HJ, Youn TJ, et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve. *J Am Coll Cardiol*. 2005;46:633-637.
 38. Ormiston JA, Currie E, Webster MW, et al. Drug-eluting stents for coronary bifurcations: insights into the crush technique. *Catheter Cardiovasc Interv*. 2004;63:332-336.
 39. Brunel P, Lefevre T, Darremont O, Louvard Y. Provisional T-stenting and kissing balloon in the treatment of coronary bifurcation lesions: results of the French multicenter "TULIPE" study. *Catheter Cardiovasc Interv*. 2006;68:67-73.
 41. Niemela M, Kervinen K, Erglis A, et al. Randomized comparison of final kissing balloon dilatation versus no final kissing balloon dilatation in patients with coronary bifurcation lesions treated with main vessel stenting: the Nordic-Baltic Bifurcation Study III. *Circulation*. 2011;123:79-86.
 42. Pan M, Medina A, Suarez de Lezo J, et al. Coronary bifurcation lesions treated with simple approach (from the Cordoba & Las Palmas [CORPAL] Kiss Trial). *Am J Cardiol*. 2011;107:1460-1465.
 43. Korn HV, Yu J, Ohlow MA, et al. Interventional therapy of bifurcation lesions: a TIMI flow-guided concept to treat side branches in bifurcation lesions—a prospective randomized clinical study (Thueringer bifurcation study, THUEBIS study as pilot trial). *Circ Cardiovasc Interv*. 2009;2:535-542.
 45. Gwon HC, Hahn JY, Koo BK, et al. Final kissing ballooning and long-term clinical outcomes in coronary bifurcation lesions treated with 1-stent technique: results from the COBIS registry. *Heart*. 2012;98:225-231.
 46. Zhong M, Tang B, Zhao Q, Cheng J, Jin Q, Fu S. Should kissing balloon inflation after main vessel stenting be routine in the one-stent approach? A systematic review and meta-analysis of randomized trials. *PloS One*. 2018;13:e0197580.
 47. Hildick-Smith D, Arunothayaraj S, Stankovic G, Chen SL. Percutaneous coronary intervention of bifurcation lesions. *EuroIntervention*. 2022;18:e273-e291.
 48. Mylotte D, Hovasse T, Ziani A, et al. Non-compliant balloons for final kissing inflation in coronary bifurcation lesions treated with provisional side branch stenting: a pilot study. *EuroIntervention*. 2012;7:1162-1169.
 51. Adriaenssens T, Byrne RA, Dibra A, et al. Culotte stenting technique in coronary bifurcation disease: angiographic follow-up using dedicated quantitative coronary angiographic analysis and 12-month clinical outcomes. *Eur Heart J*. 2008;29:2868-2876.
 53. Ormiston JA, Webster MW, Webber B, Stewart JT, Ruygrok PN, Hatrick RI. The "crush" technique for coronary artery bifurcation stenting: insights from micro-computed tomographic imaging of bench deployments. *J Am Coll Cardiol Interv*. 2008;1:351-357.
 55. Brar SS, Gray WA, Dangas G, et al. Bifurcation stenting with drug-eluting stents: a systematic review and meta-analysis of randomised trials. *EuroIntervention*. 2009;5:475-484.
 56. Katritsis DG, Siontis GC, Ioannidis JP. Double versus single stenting for coronary bifurcation lesions: a meta-analysis. *Circ Cardiovasc Interv*. 2009;2:409-415.
 57. Maeng M, Holm NR, Erglis A, et al. Long-term results after simple versus complex stenting of coronary artery bifurcation lesions: Nordic Bifurcation Study 5-year follow-up results. *J Am Coll Cardiol*. 2013;62:30-34.
 60. Kim HY, Doh JH, Lim HS, et al. Identification of coronary artery side branch supplying myocardial mass that may benefit from revascularization. *JACC Cardiovasc Interv*. 2017;10:571-581.
 64. Naganuma T, Chieffo A, Basavarajiah S, et al. Single-stent crossover technique from distal unprotected left main coronary artery to the left circumflex artery. *Catheter Cardiovasc Interv*. 2013;82:757-764.
 65. Chen SL, Zhang JJ, Han Y, et al. Double kissing crush versus provisional stenting for left main distal bifurcation lesions: DKCRUSH-V Randomized Trial. *J Am Coll Cardiol*. 2017;70:2605-2617.
 66. Chen X, Li X, Zhang JJ, et al. 3-year outcomes of the DKCRUSH-V trial comparing DK crush with provisional stenting for left main bifurcation lesions. *JACC Cardiovasc Interv*. 2019;12:1927-1937.
 67. Hildick-Smith D, Egred M, et al. The European bifurcation club Left Main Coronary Stent study: a randomized comparison of stepwise provisional vs. systematic dual stenting strategies (EBC MAIN). *Eur Heart J*. 2021;42:3829-3839.
 68. Kini AS, Dangas GD, Baber U, et al. Influence of final kissing balloon inflation on long-term outcomes after PCI of distal left main bifurcation lesions in the EXCEL trial. *EuroIntervention*. 2020;16:218-224.
 69. Chen SL, Xu B, Han YL, et al. Comparison of double kissing crush versus Culotte stenting for unprotected distal left main bifurcation lesions: results from a multicenter, randomized, prospective DKCRUSH-III study. *J Am Coll Cardiol*. 2013;61:1482-1488.
 70. Chen SL, Xu B, Han YL, et al. Clinical outcome after DK crush versus culotte stenting of distal left main bifurcation lesions: the 3-year follow-up results of the DKCRUSH-III study. *JACC Cardiovasc Interv*. 2015;8:1335-1342.
 75. Burzotta F, De Vita M, Sgueglia G, Todaro D, Trani C. How to solve difficult side branch access? *EuroIntervention*. 2010;6(suppl J):J72-J80.
 77. Chevalier B, Mamas MA, Hovasse T, et al. Clinical outcomes of the proximal optimisation technique (POT) in bifurcation stenting. *EuroIntervention*. 2021;17:e910-e918.
 82. Erglis A, Kumsars I, Niemela M, et al. Randomized comparison of coronary bifurcation stenting with the crush versus the culotte technique using sirolimus eluting stents: the Nordic stent technique study. *Circ Cardiovasc Interv*. 2009;2:27-34.
 85. Chen SL, Zhang JJ, Ye F, et al. Study comparing the double kissing (DK) crush with classical crush for the treatment of coronary bifurcation lesions: the DKCRUSH-1 Bifurcation Study with drug-eluting stents. *Eur J Clin Invest*. 2008;38:361-371.
 94. Chen SL, Santoso T, Zhang JJ, et al. Clinical outcome of double kissing crush versus provisional stenting of coronary artery bifurcation lesions: the 5-year follow-up results from a Randomized and Multicenter DKCRUSH-II Study (Randomized Study on Double Kissing Crush Technique Versus Provisional Stenting Technique for Coronary Artery Bifurcation Lesions). *Circ Cardiovasc Interv*. 2017;10(2):e004497.
 95. Park SJ, Kim YH, Park DW, et al. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv*. 2009;2(3):167-177.
 97. de la Torre Hernandez JM, Baz Alonso JA, Gómez Hospital JA, et al. Clinical impact of intravascular ultrasound guidance in drug-eluting stent implantation for unprotected left main coronary disease: pooled analysis at the patient-level of 4 registries. *JACC Cardiovasc Interv*. 2014;7:244-254.
 98. Gao XF, Ge Z, Kong XQ, et al. 3-year outcomes of the ULTIMATE trial comparing intravascular ultrasound versus angiography-guided drug-eluting stent implantation. *JACC Cardiovasc Interv*. 2021;14:247-257.
 99. Salazar CH, Gonzalo N, Aksoy A, et al. Feasibility, safety, and efficacy of intravascular lithotripsy in severely calcified left main coronary stenosis. *JACC Cardiovasc Interv*. 2020;13:1727-1729.

REFERENCES

- Fujii K, Kobayashi Y, Mintz GS, et al. Dominant contribution of negative remodeling to development of significant coronary bifurcation narrowing. *Am J Cardiol*. 2003;92:59-61.
- Popma J, Leon M, Topol EJ. *Atlas of Interventional Cardiology*. Saunders; 1994.
- Lefevre T, Louvard Y, Morice MC, et al. Stenting of bifurcation lesions: classification, treatments, and results. *Catheter Cardiovasc Interv*. 2000;49:274-283.
- Safian RD. Bifurcation lesions. In: Safian RD, Freed M, eds. *Manual of Interventional Cardiology*. Vol 10. Physicians' Press; 2001:221-236.
- Spokojny AM, Sanborn TM. The bifurcation lesion. In: Ellis SG, Holmes DR, eds. *Strategic Approaches in Coronary Intervention*. Williams & Wilkins; 1996:288.
- Louvard Y, Lefevre T, Morice MC. Percutaneous coronary intervention for bifurcation coronary disease. *Heart*. 2004;90:713-722.
- Medina A, Suarez de Lezo J, Pan M. A new classification of coronary bifurcation lesions. *Rev Esp Cardiol*. 2006;59:183-183.
- Movahed MR, Stinis CT. A new proposed simplified classification of coronary artery bifurcation lesions and bifurcation interventional techniques. *J Invasive Cardiol*. 2006;18:199-204.
- Sianos G, Morel MA, Kappetein AP. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *Eurointervention*. 2005;1:219-227.
- Myler RK, Shaw RE, Stertz SH, et al. Lesion morphology and coronary angioplasty: current experience and analysis. *J Am Coll Cardiol*. 1992;19:1641-1652.
- Latib A, Colombo A. Bifurcation disease: what do we know, what should we do? *J Am Coll Cardiol Interv*. 2008;1:218-226.
- Iakovou I, Colombo A. Contemporary stent treatment of coronary bifurcations. *J Am Coll Cardiol*. 2005;46:1446-1455.
- Hahn JY, Chun WJ, Kim JH, et al. Predictors and outcomes of side branch occlusion after main vessel stenting in coronary bifurcation lesions: results from the COBIS II Registry (Coronary Bifurcation Stenting). *J Am Coll Cardiol*. 2013;62:1654-1659.
- Al Suwaidi J, Berger PB, Rihal CS, et al. Immediate and long-term outcome of intracoronary stent implantation for true bifurcation lesions. *J Am Coll Cardiol*. 2000;35:929-936.
- Yamashita T, Nishida T, Adamian MG, et al. Bifurcation lesions: two stents versus one stent—immediate and follow-up results. *J Am Coll Cardiol*. 2000;35:1145-1151.
- Thuesen L, Kelbaek H, Klovgaard L, et al. Comparison of sirolimus-eluting and bare metal stents in coronary bifurcation lesions: subgroup analysis of the Stenting Coronary Arteries in Non-Stress/Benestent Disease Trial (SCANDSTENT). *Am Heart J*. 2006;152:1140-1145.
- Ge L, Tsagalou E, Iakovou I, et al. In-hospital and nine-month outcome of treatment of coronary bifurcation lesions with sirolimus-eluting stent. *Am J Cardiol*. 2005;95:757-760.
- Windecker S, Latib A, Kedhi E, et al. Polymer-based versus polymer-free stents in high bleeding risk patients: final 2-year results from Onyx ONE. *JACC Cardiovasc Interv*. 2022;15:1153-1163.
- Kandzari DE, Kirtane AJ, Mehran R, et al. Clinical outcomes according to lesion complexity in high bleeding risk patients treated with 1-month dual antiplatelet therapy following PCI: analysis from the Onyx ONE clear study. *Catheter Cardiovasc Interv*. 2022;99:583-592.
- Colombo A, Moses JW, Morice MC, et al. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation*. 2004;109:1244-1249.
- Pan M, de Lezo JS, Medina A, et al. Rapamycin-eluting stents for the treatment of bifurcated coronary lesions: a randomized comparison of a simple versus complex strategy. *Am Heart J*. 2004;148:857-864.
- Steigen TK, Maeng M, Wiseth R, et al. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation*. 2006;114:1955-1961.
- Ferenc M, Gick M, Kienzle RP, et al. Randomized trial on routine vs. provisional T-stenting in the treatment of de novo coronary bifurcation lesions. *Eur Heart J*. 2008;29:2859-2867.
- Colombo A, Bramucci E, Sacca S, et al. Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurcations: the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) Study. *Circulation*. 2009;119:71-78.
- Hildick-Smith D, de Belder AJ, Cooter N, et al. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation*. 2010;121:1235-1243.
- Chen SL, Santoso T, Zhang JJ, et al. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions: results from the DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) trial. *J Am Coll Cardiol*. 2011;57:914-920.
- Kumsars I, Holm NR, Niemela M, et al. Randomised comparison of provisional side branch stenting versus a two-stent strategy for treatment of true coronary bifurcation lesions involving a large side branch: the Nordic-Baltic Bifurcation Study IV. *Open Heart*. 2020;7:e000947.
- Hildick-Smith D, Behan MW, Lassen JF, et al. The EBC TWO Study (European Bifurcation Coronary TWO): a randomized comparison of provisional T-stenting versus a systematic 2 stent culotte strategy in large caliber true bifurcations. *Circ Cardiovasc Interv*. 2016;9(9):e003643.
- Colombo A. CACTUS Trial (Coronary Bifurcation Application of the Crush Technique Using Sirolimus-Eluting Stents). Presented at Transcatheter Cardiovascular Therapeutics, Washington, DC; October 24, 2007.
- Aliabadi D, Tili FV, Bowers TR, et al. Incidence and angiographic predictors of side branch occlusion following high-pressure intracoronary stenting. *Am J Cardiol*. 1997;80:994-997.
- Furukawa E, Hibi K, Kosuge M, et al. Intravascular ultrasound predictors of side branch occlusion in bifurcation lesions after percutaneous coronary intervention. *Circ J*. 2005;69:325-330.
- Chaudhry EC, Dauerman KP, Sarnoski CL, Thomas CS, Dauerman HL. Percutaneous coronary intervention for major bifurcation lesions using the simple approach: risk of myocardial infarction. *J Thromb Thrombolysis*. 2007;24(1):7-13.
- Naganuma T, Latib A, Basavarajaiah S, et al. The long-term clinical outcome of T-stenting and small protrusion technique for coronary bifurcation lesions. *JACC Cardiovasc Interv*. 2013;6:554-561.
- Koo BK, Waseda K, Kang HJ, et al. Anatomic and functional evaluation of bifurcation lesions undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2010;3:113-119.
- Koo BK, Kang HJ, Youn TJ, et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve. *J Am Coll Cardiol*. 2005;46:633-637.
- Dauerman HL, Higgins PJ, Sparano AM, et al. Mechanical debulking versus balloon angioplasty for the treatment of true bifurcation lesions. *J Am Coll Cardiol*. 1998;32:1845-1852.
- Hermiller JB. Bifurcation intervention: keep it simple. *J Invasive Cardiol*. 2006;18:43-44.
- Ormiston JA, Currie E, Webster MW, et al. Drug-eluting stents for coronary bifurcations: insights into the crush technique. *Catheter Cardiovasc Interv*. 2004;63:332-336.
- Brunel P, Lefevre T, Darremont O, Louvard Y. Provisional T-stenting and kissing balloon in the treatment of coronary bifurcation lesions: results of the French multicenter "TULIPE" study. *Catheter Cardiovasc Interv*. 2006;68:67-73.
- Murasato Y, Iwasaki K, Yamamoto T, et al. Optimal kissing balloon inflation after single-stent deployment in a coronary bifurcation model. *Eurointervention*. 2014;10:934-941.
- Niemela M, Kervinen K, Erglis A, et al. Randomized comparison of final kissing balloon dilatation versus no final kissing balloon dilatation in patients with coronary bifurcation lesions treated with main vessel stenting: the Nordic-Baltic Bifurcation Study III. *Circulation*. 2011;123:79-86.
- Pan M, Medina A, Suarez de Lezo J, et al. Coronary bifurcation lesions treated with simple approach (from the Cordoba & Las Palmas [CORPAL] Kiss Trial). *Am J Cardiol*. 2011;107:1460-1465.
- Korn HV, Yu J, Ohlow MA, et al. Interventional therapy of bifurcation lesions: a TIMI flow-guided concept to treat side branches in bifurcation lesions—a prospective randomized clinical study (Thueringer bifurcation study, THUEBIS study as pilot trial). *Circ Cardiovasc Interv*. 2009;2:535-542.
- Lee CH, Nam CW, Cho YK, et al. 5-year outcome of simple crossover stenting in coronary bifurcation lesions compared with side branch opening. *JACC Asia*. 2021;1:53-64.
- Gwon HC, Hahn JY, Koo BK, et al. Final kissing ballooning and long-term clinical outcomes in coronary bifurcation lesions treated with 1-stent technique: results from the COBIS registry. *Heart*. 2012;98:225-231.
- Zhong M, Tang B, Zhao Q, Cheng J, Jin Q, Fu S. Should kissing balloon inflation after main vessel stenting be routine in the one-stent approach? A systematic review and meta-analysis of randomized trials. *PLoS One*. 2018;13:e0197580.
- Hildick-Smith D, Arunothayaraj S, Stankovic G, Chen SL. Percutaneous coronary intervention of bifurcation lesions. *Eurointervention*. 2022;18:e273-e291.
- Mylotte D, Hovasse T, Ziani A, et al. Non-compliant balloons for final kissing inflation in coronary bifurcation lesions treated with provisional side branch stenting: a pilot study. *Eurointervention*. 2012;7:1162-1169.
- Hoye A, Iakovou I, Ge L, et al. Long-term outcomes after stenting of bifurcation lesions with the "crush" technique: predictors of an adverse outcome. *J Am Coll Cardiol*. 2006;47:1949-1958.
- Ge L, Airolidi F, Iakovou I, et al. Clinical and angiographic outcome after implantation of drug-eluting stents in bifurcation lesions with the crush stent technique: importance of final kissing balloon post-dilatation. *J Am Coll Cardiol*. 2005;46:613-620.
- Adriaenssens T, Byrne RA, Dibra A, et al. Culotte stenting technique in coronary bifurcation disease: angiographic follow-up using dedicated quantitative coronary angiographic analysis and 12-month clinical outcomes. *Eur Heart J*. 2008;29:2868-2876.
- Ormiston JA. Drug-eluting stents for coronary bifurcations: bench testing of provisional side-branch strategies. *Catheter Cardiovasc Interv*. 2006;67:49-55.
- Ormiston JA, Webster MW, Webber B, Stewart JT, Ruygrok PN, Hatrick RI. The "crush" technique for coronary artery bifurcation stenting: insights from micro-computed tomographic imaging of bench deployments. *J Am Coll Cardiol Interv*. 2008;1:351-357.
- Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293:2126-2130.
- Brar SS, Gray WA, Dangas G, et al. Bifurcation stenting with drug-eluting stents: a systematic review and meta-analysis of randomised trials. *Eurointervention*. 2009;5:475-484.
- Katritsis DG, Siontis GC, Ioannidis JP. Double versus single stenting for coronary bifurcation lesions: a meta-analysis. *Circ Cardiovasc Interv*. 2009;2:409-415.



57. Maeng M, Holm NR, Erglis A, et al. Long-term results after simple versus complex stenting of coronary artery bifurcation lesions: Nordic Bifurcation Study 5-year follow-up results. *J Am Coll Cardiol*. 2013;62:30-34.
58. Ong AT, Hoyer A, Aoki J, et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J Am Coll Cardiol*. 2005;45:947-953.
59. Armstrong EJ, Yeo KK, Javed U, et al. Angiographic stent thrombosis at coronary bifurcations: short- and long-term prognosis. *JACC Cardiovasc Interv*. 2012;5:57-63.
60. Kim HY, Doh JH, Lim HS, et al. Identification of coronary artery side branch supplying myocardial mass that may benefit from revascularization. *JACC Cardiovasc Interv*. 2017;10:571-581.
61. Louvard Y, Lefevre T. Bifurcation lesion stenting. In: Colombo A, Stankovic G, eds. *Problem Oriented Approaches in Interventional Cardiology*. Informa Healthcare; 2007:37-57.
62. Louvard Y, Thomas M, Dzavik V et al. Classification of coronary artery bifurcation lesions and treatments: time for a consensus! *Catheter Cardiovasc Interv*. 2008;71:175-183.
63. Sato K, Naganuma T, Costopoulos C, et al. Calcification analysis by intravascular ultrasound to define a predictor of left circumflex narrowing after cross-over stenting for unprotected left main bifurcation lesions. *Cardiovasc Revasc Med*. 2014;15:80-85.
64. Naganuma T, Chieffo A, Basavarajiah S, et al. Single-stent crossover technique from distal unprotected left main coronary artery to the left circumflex artery. *Catheter Cardiovasc Interv*. 2013;82:757-764.
65. Chen SL, Zhang JJ, Han Y, et al. Double kissing crush versus provisional stenting for left main distal bifurcation lesions: DKCRUSH-V Randomized Trial. *J Am Coll Cardiol*. 2017;70:2605-2617.
66. Chen X, Li X, Zhang JJ, et al. 3-year outcomes of the DKCRUSH-V trial comparing DK crush with provisional stenting for left main bifurcation lesions. *JACC Cardiovasc Interv*. 2019;12:1927-1937.
67. Hildick-Smith D, Egred M, et al. The European bifurcation club Left Main Coronary Stent study: a randomized comparison of stepwise provisional vs. systematic dual stenting strategies (EBC MAIN). *Eur Heart J*. 2021;42:3829-3839.
68. Kini AS, Dangas GD, Baber U, et al. Influence of final kissing balloon inflation on long-term outcomes after PCI of distal left main bifurcation lesions in the EXCEL trial. *EuroIntervention*. 2020;16:218-224.
69. Chen SL, Xu B, Han YL, et al. Comparison of double kissing crush versus Culotte stenting for unprotected distal left main bifurcation lesions: results from a multicenter, randomized, prospective DKCRUSH-III study. *J Am Coll Cardiol*. 2013;61:1482-1488.
70. Chen SL, Xu B, Han YL, et al. Clinical outcome after DK crush versus culotte stenting of distal left main bifurcation lesions: the 3-year follow-up results of the DKCRUSH-III study. *JACC Cardiovasc Interv*. 2015;8:1335-1342.
71. Chung S, Her SH, Song PS, et al. Trans-radial versus trans-femoral intervention for the treatment of coronary bifurcations: results from Coronary Bifurcation Stenting Registry. *J Korean Med Sci*. 2013;28:388-395.
72. Choi YJ, Lee SJ, Kim BK, et al. Effect of wire jailing at side branch in 1-stent strategy for coronary bifurcation lesions. *JACC Cardiovasc Interv*. 2022;15:443-455.
73. Arora RR, Raymond RE, Dimas AP, Bhadwar K, Simpfordorfer C. Side branch occlusion during coronary angioplasty: incidence, angiographic characteristics, and outcome. *Cathet Cardiovasc Diagn*. 1989;18:210-212.
74. Weinstein JS, Baim DS, Sipperly ME, McCabe CH, Lorell BH. Salvage of branch vessels during bifurcation lesion angioplasty: acute and long-term follow-up. *Cathet Cardiovasc Diagn*. 1991;22:1-6.
75. Burzotta F, De Vita M, Sgueglia G, Todaro D, Trani C. How to solve difficult side branch access? *EuroIntervention*. 2010;6(suppl J):J72-J80.
76. Lefevre T, Darremont O, Albiero R. Provisional side branch stenting for the treatment of bifurcation lesions. *EuroIntervention*. 2010;6(suppl J):J65-J71.
77. Chevalier B, Mamas MA, Hovasse T, et al. Clinical outcomes of the proximal optimisation technique (POT) in bifurcation stenting. *EuroIntervention*. 2021;17:e910-e918.
78. Foin N, Torii R, Mortier P, et al. Kissing balloon or sequential dilation of the side branch and main vessel for provisional stenting of bifurcations: lessons from micro-computed tomography and computational simulations. *JACC Cardiovasc Interv*. 2012;5:47-56.
79. Chevalier B, Glatt B, Royer T, Guyon P. Placement of coronary stents in bifurcation lesions by the "culotte" technique. *Am J Cardiol*. 1998;82:943-949.
80. Favero L, Pacchioni A, Reimers B. Elective double stenting for non-left main coronary artery bifurcation lesions: patient selection and technique. In: Moussa I, Colombo A, eds. *Tips and Tricks in Interventional Therapy of Coronary Bifurcation Lesions*. Informa Healthcare; 2010:83-115.
81. Latib A, Chieffo A, Colombo A. Elective double stenting for left main coronary artery bifurcation lesions: patient selection and technique. In: Moussa I, Colombo A, eds. *Tips and Tricks in Interventional Therapy of Coronary Bifurcation Lesions*. Informa Healthcare; 2010:149-192.
82. Erglis A, Kumsars I, Niemela M, et al. Randomized comparison of coronary bifurcation stenting with the crush versus the culotte technique using sirolimus eluting stents: the Nordic stent technique study. *Circ Cardiovasc Interv*. 2009;2:27-34.
83. Colombo A, Stankovic G, Orlic D, et al. Modified T-stenting technique with crushing for bifurcation lesions: immediate results and 30-day outcome. *Catheter Cardiovasc Interv*. 2003;60:145-151.
84. Galassi AR, Colombo A, Buchbinder M, et al. Long-term outcomes of bifurcation lesions after implantation of drug-eluting stents with the "mini-crush technique." *Catheter Cardiovasc Interv*. 2007;69:976-983.
85. Chen SL, Zhang JJ, Ye F, et al. Study comparing the double kissing (DK) crush with classical crush for the treatment of coronary bifurcation lesions: the DKCRUSH-1 Bifurcation Study with drug-eluting stents. *Eur J Clin Invest*. 2008;38:361-371.
86. Dzavik V, Kharbada R, Ivanov J, et al. Predictors of long-term outcome after crush stenting of coronary bifurcation lesions: importance of the bifurcation angle. *Am Heart J*. 2006;152:762-769.
87. Schampaert E, Fort S, Adelman AG, Schwartz L. The V-stent: a novel technique for coronary bifurcation stenting. *Cathet Cardiovasc Diagn*. 1996;39:320-326.
88. Sharma SK. Simultaneous kissing drug-eluting stent technique for percutaneous treatment of bifurcation lesions in large-size vessels. *Catheter Cardiovasc Interv*. 2005;65:10-16.
89. Baim DS. Editorial comment: is bifurcation stenting the answer? *Cathet Cardiovasc Diagn*. 1996;37:314-316.
90. Costa RA, Mintz GS, Carlier SG, et al. Bifurcation coronary lesions treated with the "crush" technique: an intravascular ultrasound analysis. *J Am Coll Cardiol*. 2005;46:599-605.
91. Kim SH, Kim YH, Kang SJ, et al. Long-term outcomes of intravascular ultrasound-guided stenting in coronary bifurcation lesions. *Am J Cardiol*. 2010;106:612-618.
92. Kim JS, Hong MK, Ko YG, et al. Impact of intravascular ultrasound guidance on long-term clinical outcomes in patients treated with drug-eluting stent for bifurcation lesions: data from a Korean multicenter bifurcation registry. *Am Heart J*. 2011;161:180-187.
93. Chen SL, Ye F, Zhang JJ, et al. Intravascular ultrasound-guided systematic two-stent techniques for coronary bifurcation lesions and reduced late stent thrombosis. *Catheter Cardiovasc Interv*. 2013;81:456-463.
94. Chen SL, Santoso T, Zhang JJ, et al. Clinical outcome of double kissing crush versus provisional stenting of coronary artery bifurcation lesions: the 5-year follow-up results from a Randomized and Multicenter DKCRUSH-II Study (Randomized Study on Double Kissing Crush Technique Versus Provisional Stenting Technique for Coronary Artery Bifurcation Lesions). *Circ Cardiovasc Interv*. 2017;10(2):e004497.
95. Park SJ, Kim YH, Park DW, et al. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv*. 2009;2(3):167-177.
96. Chieffo A, Park SJ, Meliga E, et al. Late and very late stent thrombosis following drug-eluting stent implantation in unprotected left main coronary artery: a multicentre registry. *Eur Heart J*. 2008;29:2108-2115.
97. de la Torre Hernandez JM, Baz Alonso JA, Gómez Hospital JA, et al. Clinical impact of intravascular ultrasound guidance in drug-eluting stent implantation for unprotected left main coronary disease: pooled analysis at the patient-level of 4 registries. *JACC Cardiovasc Interv*. 2014;7:244-254.
98. Gao XF, Ge Z, Kong XQ, et al. 3-year outcomes of the ULTIMATE trial comparing intravascular ultrasound versus angiography-guided drug-eluting stent implantation. *JACC Cardiovasc Interv*. 2021;14:247-257.
99. Salazar CH, Gonzalo N, Aksoy A, et al. Feasibility, safety, and efficacy of intravascular lithotripsy in severely calcified left main coronary stenosis. *JACC Cardiovasc Interv*. 2020;13:1727-1729.
100. Zheng Y, Li J, Wang L, et al. Effect of drug-coated balloon in side branch protection for de novo coronary bifurcation lesions: a systematic review and meta-analysis. *Front Cardiovasc Med*. 2021;8:758560.
101. Jing QM, Zhao X, Han YL, et al. A drug-eluting Balloon for the treatment of coronary bifurcation lesions in the side branch: a prospective multicenter randomized (BEYOND) clinical trial in China. *Chin Med J (Engl)*. 2020;133:899-908.



11

Bypass Graft Interventions

EMMANOUIL S. BRILAKIS AND SUBHASH BANERJEE

INTRODUCTION, 206

EPIDEMIOLOGY, 206

INDICATIONS FOR BYPASS GRAFT INTERVENTIONS, 206

DISTAL EMBOLIZATION AND EMBOLIC PROTECTION DEVICES, 208

SAPHENOUS VEIN GRAFT STENTING, 213

ADJUNCTIVE PHARMACOTHERAPY, 214

TECHNICAL ASPECTS OF SAPHENOUS VEIN GRAFT PERCUTANEOUS CORONARY INTERVENTION: INTRAVASCULAR IMAGING, 214

SAPHENOUS VEIN GRAFT ENGAGEMENT, 214

ACUTELY OCCLUDED SAPHENOUS VEIN GRAFTS, 214

CHRONICALLY OCCLUDED SAPHENOUS VEIN GRAFTS, 215

INTERMEDIATE SAPHENOUS VEIN GRAFT LESIONS, 217

SAPHENOUS VEIN GRAFT PERCUTANEOUS CORONARY INTERVENTION COMPLICATIONS, 217

ARTERIAL GRAFT INTERVENTIONS, 217

COMPLICATIONS OF PERCUTANEOUS CORONARY INTERVENTION IN PRIOR CORONARY ARTERY BYPASS GRAFTING PATIENTS, 217

INTRODUCTION

Two types of grafts are currently used for coronary artery bypass grafting (CABG): saphenous vein grafts (SVGs) and arterial grafts (internal mammary artery grafts [IMAs], radial artery grafts, and gastroepiploic grafts). IMA grafts have the best long-term patency rates,^{1,2} but in most cases, SVGs are still being used to bypass all coronary arteries that need revascularization. SVGs have high rates of failure³⁻⁵ that accelerates with increasing time after CABG (Figure 11.1).^{2,6}

EPIDEMIOLOGY

Angina in patients with prior CABG can be caused by native coronary artery disease progression, bypass graft disease, or development of proximal subclavian artery stenosis (see Figure 11.1). In an analysis from the National Cardiovascular Data Registry (NCDR), 17.5% of all percutaneous coronary interventions (PCIs) performed between 2004 and 2009 were done in prior CABG patients (300,902 of 1,721,046, 17.5% of the total PCI volume).⁶ The PCI target vessels were a native coronary artery in 62.5% and a bypass graft in 37.5% of cases. Bypass graft PCI represented 6.6% of all PCIs⁶ and was mainly performed in SVGs (6.1% of all PCIs), less commonly in arterial grafts (0.44% of all PCIs), and rarely in both arterial graft and SVG PCIs (0.04% of all PCIs). The proportion of SVGs as PCI target vessels increased after 5 years and even more so after 10 years from CABG (Figure 11.2). From January 1, 2010, through June 2011, bypass graft and SVG PCI constituted 6.0% and 5.5%, respectively, of the total NCDR PCI volume.⁷

INDICATIONS FOR BYPASS GRAFT INTERVENTIONS

Patients who present with bypass graft failure can be treated with redo CABG, medical therapy, PCI of a native coronary artery, or PCI of a bypass graft.

Redo CABG is infrequently performed because of its high morbidity and mortality rates.^{8,9} Redo CABG can also cause injury of patent grafts, which is especially concerning for IMA grafts. In the AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) trial, the risk for subsequent clinical events was similar after redo CABG and after PCI.¹⁰ According to the 2021 American College of Cardiology/American Heart Association (ACC/AHA) PCI guidelines, “if PCI is not an option, if a patent IMA to LAD is not present, or if an IMA is available to be used as a conduit for the LAD, CABG is often chosen as the revascularization strategy in patients with previous CABG and refractory angina who are at an acceptable risk for reoperation”.¹¹ Factors favoring PCI over CABG include limited areas of ischemia causing symptoms, suitable PCI targets, a patent graft to the left anterior descending artery, poor CABG targets, and comorbid conditions.¹¹ The 2018 European Society of Cardiology/European Association of Cardiothoracic Surgery (ESC/EACS) guidelines on myocardial revascularization state that if considered safe, PCI should be considered as the first choice over CABG when repeat revascularization is needed in prior CABG patients (Class IIa; level of evidence C).¹² They also suggest that the IMA is the conduit of choice for redo CABG in patients in whom it was not used previously (Class I; level of evidence B) and that redo CABG should be considered for patients without a patent IMA graft to the left anterior descending coronary artery (Class IIa; level of evidence B).¹²

In patients with SVG lesions, native coronary artery PCI is preferred over SVG PCI supplying the same territory because of better short-⁶ and long-term¹³⁻¹⁶ outcomes, especially in diffusely diseased and degenerated SVGs (Class IIa, level of evidence C in the ESC/EACS guidelines on myocardial revascularization).¹² A native coronary artery was the target vessel in the majority of prior CABG patients undergoing PCI in the NCDR.⁶ However, native coronary arteries supplied by a failing SVG can be complex (with severe calcification or chronic total occlusions [CTOs]), and challenging to recanalize.¹⁷ The choice revascularization modality and target lesion in patients presenting with SVG lesions depend on the complexity of

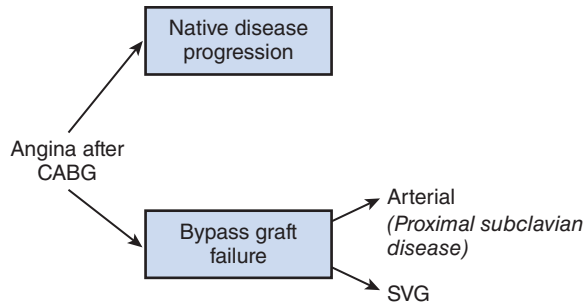


FIGURE 11.1 Potential causes of angina in prior coronary artery bypass grafting (CABG) patients. SVG, Saphenous vein graft.

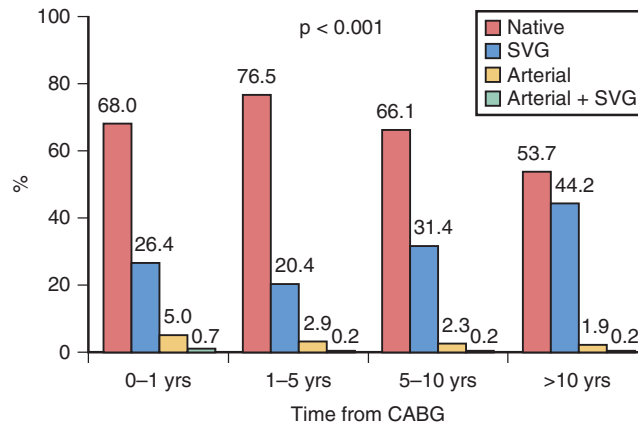


FIGURE 11.2 Comparison of the percutaneous coronary intervention target vessel in patients with prior coronary artery bypass grafting (CABG) during different time intervals from CABG, showing significant increase in the proportion of saphenous vein graft (SVG) interventions with increasing time from CABG. (Reproduced with permission from Brilakis ES, Rao SV, Banerjee S, et al. Percutaneous coronary intervention in native arteries versus bypass grafts in prior coronary artery bypass grafting patients a report from the national cardiovascular data registry. *JACC Cardiovasc Interv.* 2011;4:844-850.)

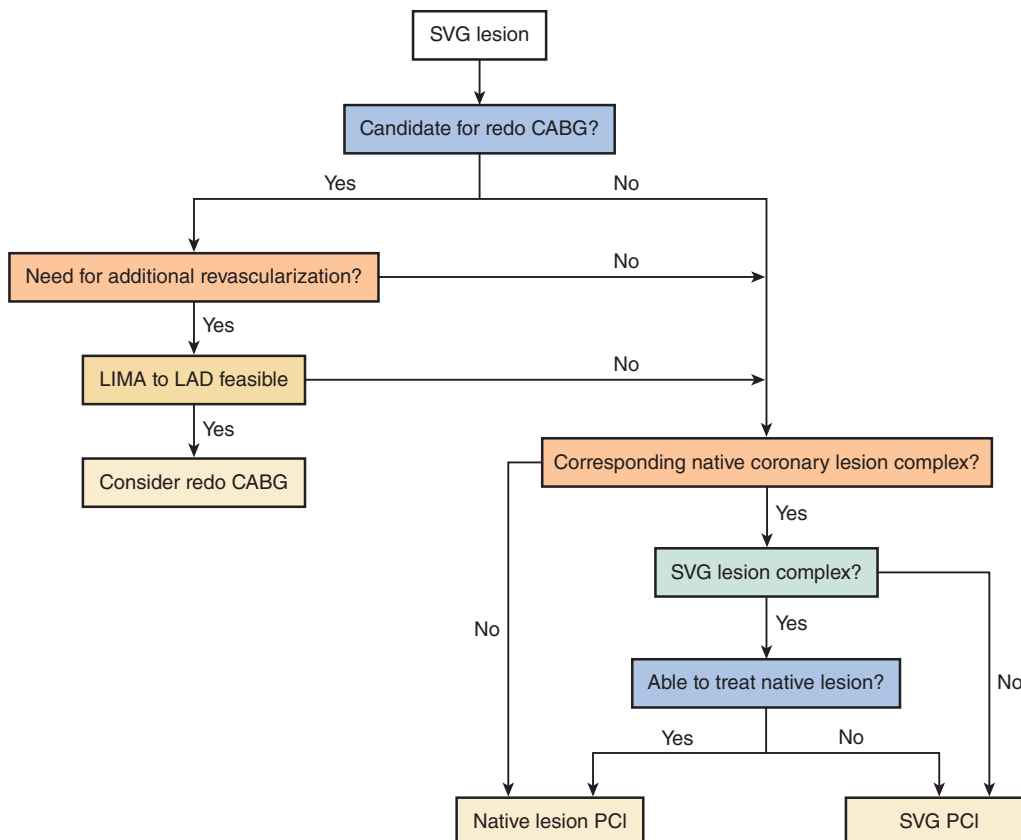


FIGURE 11.3 Revascularization options in prior coronary artery bypass graft (CABG) patients presenting with saphenous vein graft (SVG) lesions. LAD, left anterior descending coronary artery; LIMA, left internal mammary artery; PCI, percutaneous coronary intervention. (Reproduced with permission from Xenogiannis I, Tajti P, Hall AB, et al. Update on cardiac catheterization in patients with prior coronary artery bypass graft surgery. *JACC Cardiovasc Interv.* 2019;12:1635-1649.)

be treated with PCI of the corresponding native coronary artery, followed by occlusion of the SVG with coils or with an Amplatzer vascular plug.²⁶ A strategy of native coronary instead of SVG PCI is currently being evaluated in the PROCTOR (Percutaneous Coronary Intervention of Native Coronary Artery Versus Venous Bypass Graft in Patients With Prior CABG; NCT03805048) clinical trial.

Saphenous vein graft PCI has two major limitations: (a) high rates of distal embolization and (b) high rates of in-stent restenosis, which are discussed in subsequent sections. Patients undergoing SVG PCI are usually older

and have more comorbidities than patients undergoing native coronary artery PCI²⁷ and as a result have high risk for both periprocedural and subsequent events (both cardiovascular and noncardiovascular).

DISTAL EMBOLIZATION AND EMBOLIC PROTECTION DEVICES

Saphenous vein graft lesions can have complex morphology (Figure 11.4) and friable atheromas²⁸ that can result in

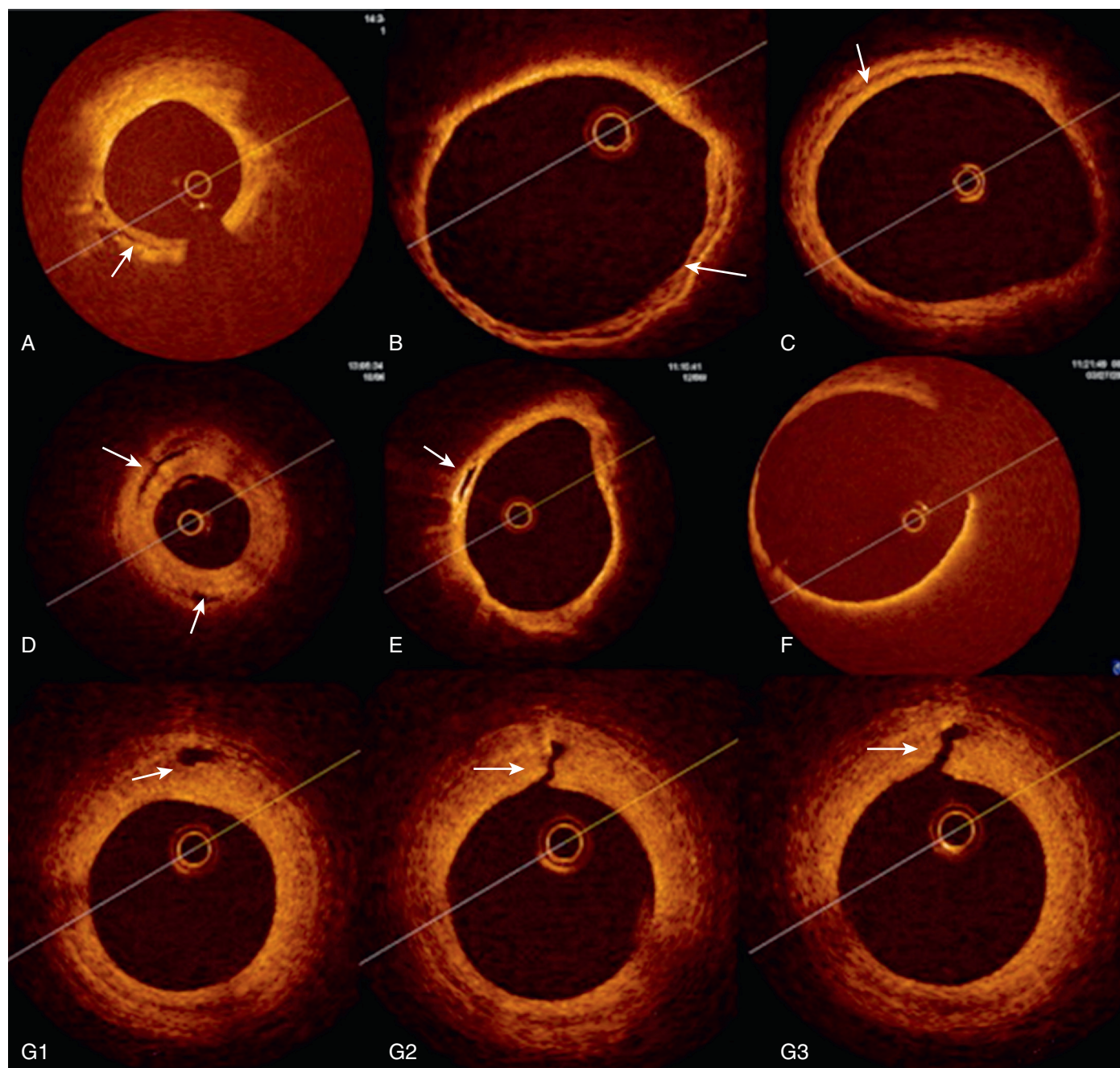


FIGURE 11.4 Optical coherence tomography findings in saphenous vein grafts (SVGs) from patients presenting with acute coronary syndromes. **A to D**, Arrows point to signal-free zones inside the walls of SVGs. Over these zones, signal-rich tissue is loosely adherent to the SVG walls. As such, images correspond to areas of severe angiographic degeneration; they are considered an indication of SVG friable tissue. **E**, Arrow points to a signal-free “microcavity,” which may represent neovascularization or tissue rupture. **G1 to G3**, Three successive optical coherence tomography frames depicting tissue rupture with communication of a small cavity with the SVG lumen. In **B** and **F**, the walls of the SVG look very thin with severe circumferential signal attenuation that is probably related to its tissue composition, which was given the name “sun eclipse.” (Reproduced with permission from Davlouros P, Damelou A, Karantalis V, et al. Evaluation of culprit saphenous vein graft lesions with optical coherence tomography in patients with acute coronary syndromes. *JACC Cardiovasc Interv*. 2011;4:683-693.)

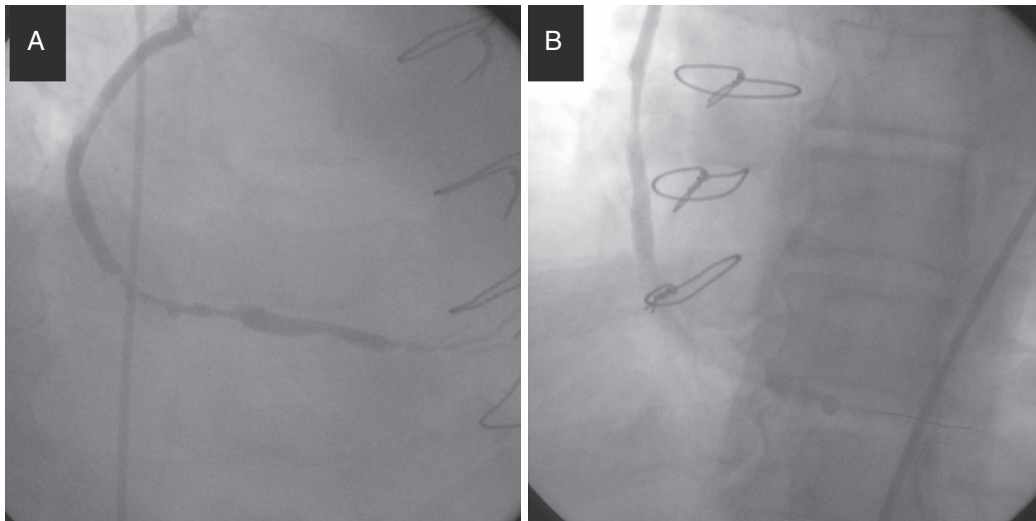


FIGURE 11.5 Example of no reflow during saphenous vein graft (SVG) intervention. No reflow with severe chest pain and ST-segment elevation occurred after crossing of a degenerated SVG (**A** and **Video 11.1**) with a FilterWire (**B** and **Video 11.2**).

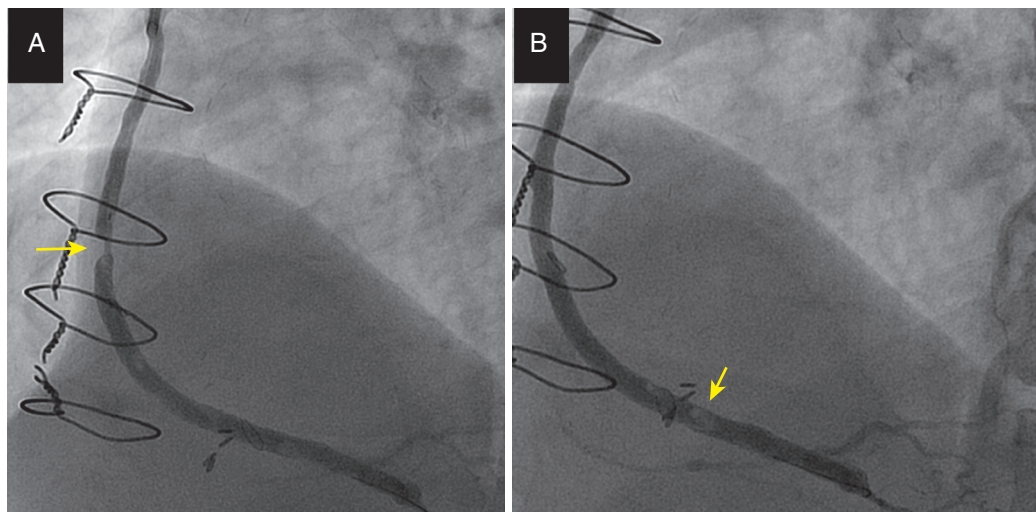


FIGURE 11.6 Example of debris capture by a filter. A FilterWire was placed distally to an eccentric saphenous vein graft body lesion (**A** and **Video 11.3**). During percutaneous coronary intervention, debris embolized distally and was captured within the filter (arrow, **B** and **Video 11.4**).

▶ distal embolization during PCI (**Figures 11.5 to 11.7** and **Videos 11.1 to 11.4**).^{29,30} Distal embolization can cause no reflow and acute ST-segment elevation or present as asymptomatic cardiac biomarker elevation. Cardiac biomarker elevation after SVG PCI (especially creatine kinase-MB increase more than five times the upper limit of normal) has been associated with increased mortality rates³¹; hence, it is important to prevent distal embolization or promptly treat it if it occurs.

Use of an embolic protection device (EPD) is the only strategy for preventing distal embolization during SVG PCI that has been shown to provide benefit in randomized controlled trials (RCTs). EPDs capture debris liberated during PCI before they enter the coronary microcirculation, causing injury. As of 2023, two EPDs are available in the United States (**Figure 11.8** and **Table 11.1**), the FilterWire (Boston Scientific) and the Spider (Medtronic Vascular). Both devices require meticulous technique for maximizing the potential benefits and minimizing the device-associated risks (how-to-use videos for FilterWire: <https://youtu.be/HgSJpeY8MKo> and Spider: <https://youtu.be/A2guiZ3nUwM>).

The SAFER (Saphenous vein graft Angioplasty Free of Emboli Randomized) trial randomized 801 patients undergoing SVG PCI to Guardwire (guidewire with a balloon at its distal segment stopping antegrade flow during SVG PCI followed by aspiration of any liberated debris before deflation) or stenting over a standard guidewire.³² The study's primary endpoint (composite of death, myocardial infarction [MI], emergency CABG, or target lesion revascularization [TLR] by 30 days) occurred in 65 patients (16.5%) assigned to control versus 39 patients (9.6%) assigned to the Guardwire ($P = .004$). This significant 42% relative reduction in the primary endpoint was driven by a reduction in the incidence of MI (8.6% vs 14.7%; $P = .008$). No reflow was also less common in the EPD group (3% vs 9%; $P = .02$). Given the significant clinical benefit with EPD use, subsequent SVG PCI studies used a noninferiority design to compare one EPD with another, as summarized in **Table 11.2**.³³⁻³⁷

Choosing an EPD for a specific SVG lesion is based on several factors, such as lesion location, device availability, local expertise in EPD use, and the potential hemodynamic consequences of SVG flow cessation (**Figure 11.9**). Although

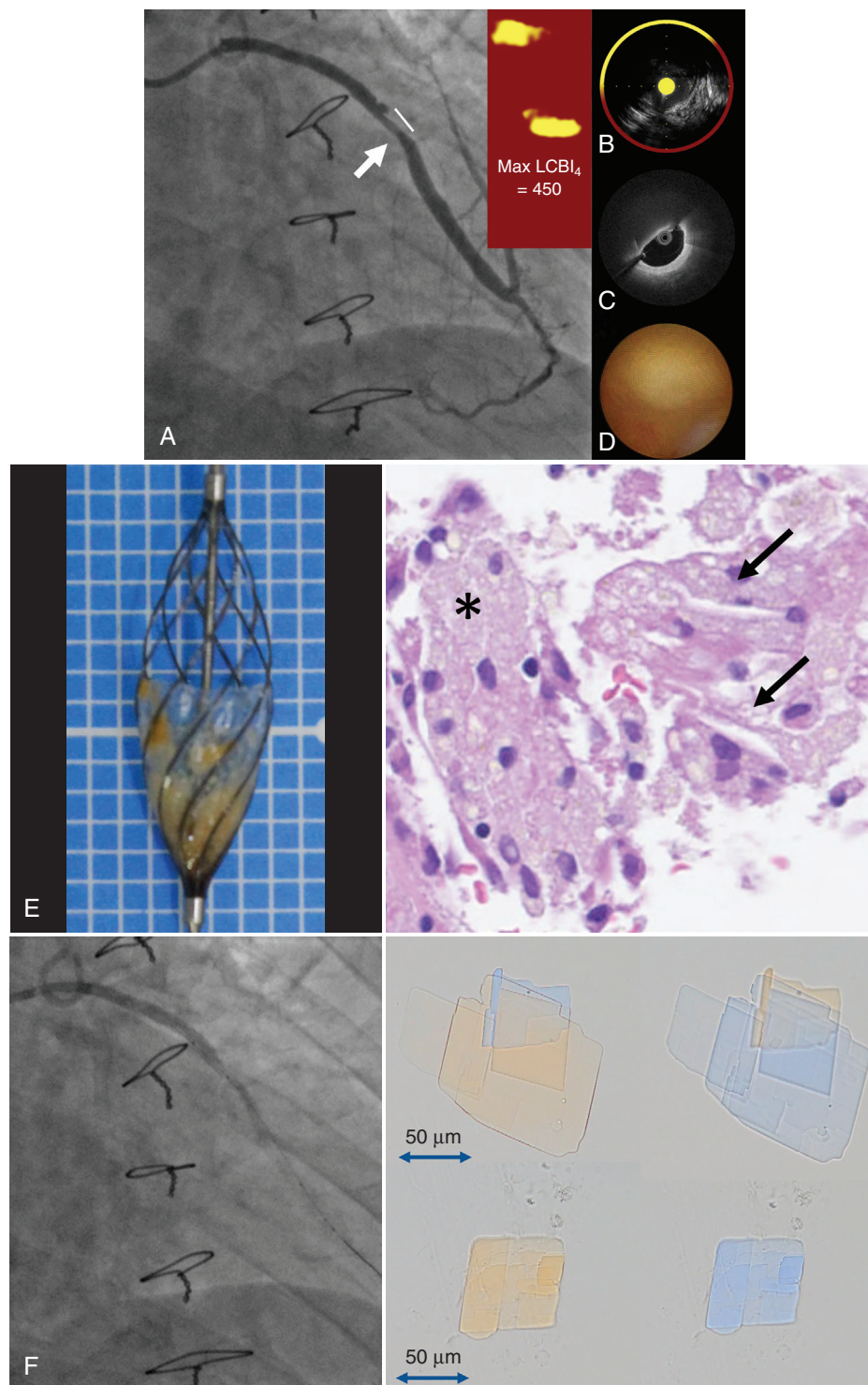


FIGURE 11.7 Use of a filter during saphenous vein graft (SVG) intervention. **A**, Angiography of the diseased SVG with significant stenosis (arrow); maximal lipid core burden index (LCBI₄) was 450 by near-infrared spectroscopy (NIRS). **B**, NIRS intravascular ultrasound imaging shows 62% plaque burden. **C**, Optical coherence tomography shows a large lipid core and a thin cap (85 μm). **D**, Angiography shows intense yellow plaque. **E**, Collected atheromatous debris (left). Microscopic observation (right) with hematoxylin and eosin staining showed an aggregation of foam cells (asterisk) and ghost images of cholesterol crystals (arrow). **F**, Blood aspiration with filter-no-reflow phenomenon (left). Cholesterol crystals are shown as blue or orange according to the direction of polarized light (right).

Device	Manufacturer	Approval date
FilterWire	Boston Scientific	June 2003
Spider	ev3	June 2006

FIGURE 11.8 Embolic protection devices available for saphenous vein graft interventions in the United States.

TABLE 11.1 Description of Various Embolic Protection Devices Available for Clinical Use in the United States in 2021

DEVICE	DESIGN	GUIDE CATHETER (Fr)	PORE SIZE	DIAMETER (MM)	CROSSING PROFILE (Fr)	LANDING ZONE
FilterWire	Polyurethane filter basket	6	110 μ m	2.25–3.5 and 3.5–5.5	3.2	$\geq$ 25 mm (2.25) or $\geq$ 30 mm (3.5)
Spider	Nitinol mesh, filter coated with heparin	6	70- μ m distal end, 165- μ m mid, 200- μ m proximal end	3, 4, 5, 6, and 7	3.2	$\geq$ 40–50 mm

TABLE 11.2 Trials of Embolic Protection Devices in Saphenous Vein Graft Percutaneous Coronary Intervention

TRIAL NAME	YEAR	PATIENTS (n)	PRIMARY ENDPOINT	EPD EVENT RATE (%)	CONTROL GROUP EVENT RATE (%)	P SUPERIORITY
EPD vs no EPD						
SAFER ³²	2002	801	30-day composite of death, MI, emergency CABG, or TLR	Guardwire (Medtronic Vascular): 9.6	16.5	.004
One EPD vs another EPD				TEST EPD EVENT RATE (%)	CONTROL EPD EVENT RATE (%)	P NONINFERIORITY
FIRE ³³	2003	651	30-day composite of death, MI, or TVR	9.9 (FilterWire, Boston Scientific)	11.6 (Guardwire)	.0008
SPIDER	2005	732	30-day composite of death, MI, urgent CABG, or TVR	9.1 (Spider, ev3)	8.4 (Guardwire 24% or FilterWire 76%)	.012
PRIDE ³⁴	2005	631	30-day composite of cardiac death, MI, or TLR	11.2 (Triactiv, Kensey Nash Corp.)	10.1 (FilterWire)	.02
CAPTIVE ³⁵	2006	652	30-day composite of death, MI, or TVR	11.4 (CardioShield, MedNova)	9.1 (Guardwire)	.057
PROXIMAL ³⁶	2007	594	30-day composite of death, MI, or TVR	9.2 (Proxis, St. Jude Medical)	10.0 (Guardwire 19% or FilterWire 81%)	.006
AMETHYST ³⁷	2008	797	30-day composite of death, MI, or urgent repeat revascularization	8.0 (Interceptor Plus, Medtronic Vascular)	7.3 (Guardwire 72% or FilterWire 18%)	.025

AMETHYST, Assessment of the Medtronic AVE Interceptor Saphenous Vein Graft Filter System; *CABG*, coronary artery bypass graft surgery; *CAPTIVE*, CardioShield Application Protects during Transluminal Intervention of Vein grafts by reducing Emboli; *EPD*, embolic protection device; *FIRE*, FilterWire EX Randomized Evaluation; *MI*, myocardial infarction; *PRIDE*, Protection During Saphenous Vein Graft Intervention to Prevent Distal Embolization; *PROXIMAL*, Proximal Protection During Saphenous Vein Graft Intervention; *SAFER*, Saphenous vein graft Angioplasty Free of Emboli Randomized; *SPIDER*, Saphenous Vein Graft Protection In a Distal Embolic Protection Randomized Trial; *TLR*, target lesion revascularization; *TVR*, target vessel revascularization.

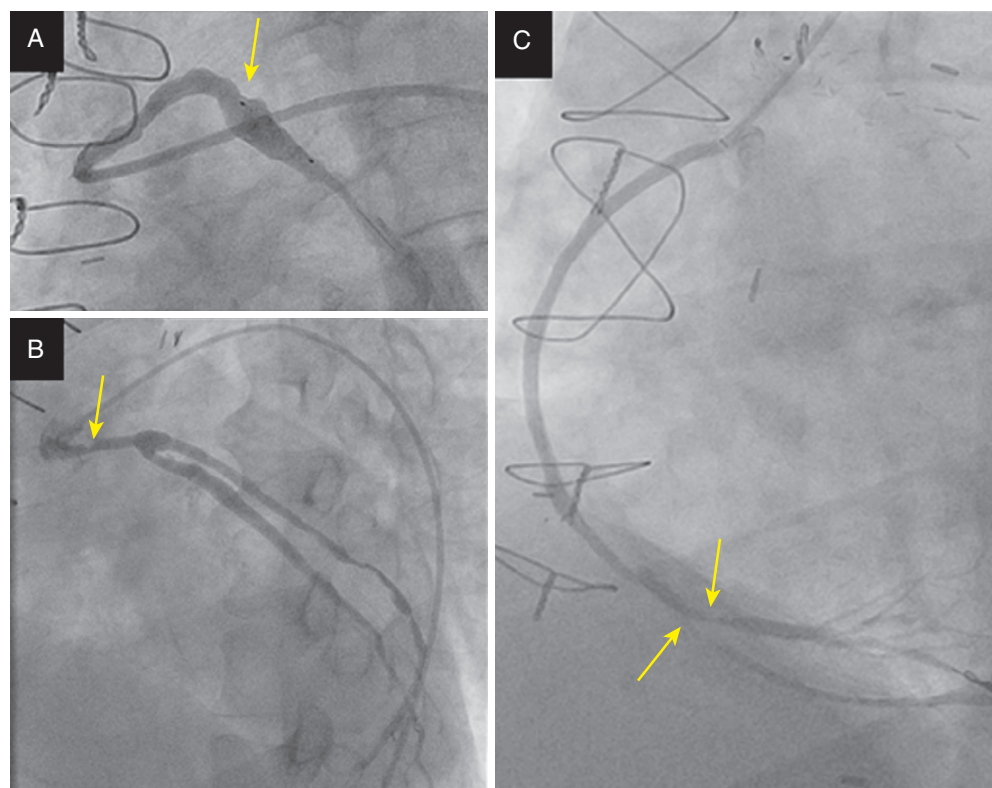


FIGURE 11.9 Saphenous vein graft (SVG) lesions in which an embolic protection device could not be used because of large caliber of the graft (**A**) or lesion proximal to a Y-graft bifurcation (**B**) or because of location at the distal SVG anastomosis (**C**). (Reproduced with permission from Brilakis ES. Bypass graft intervention and embolic protection. In: Kern MJ, ed. *SCAI Interventional Cardiology Board Review*. Lippincott Williams & Wilkins, 2014.)

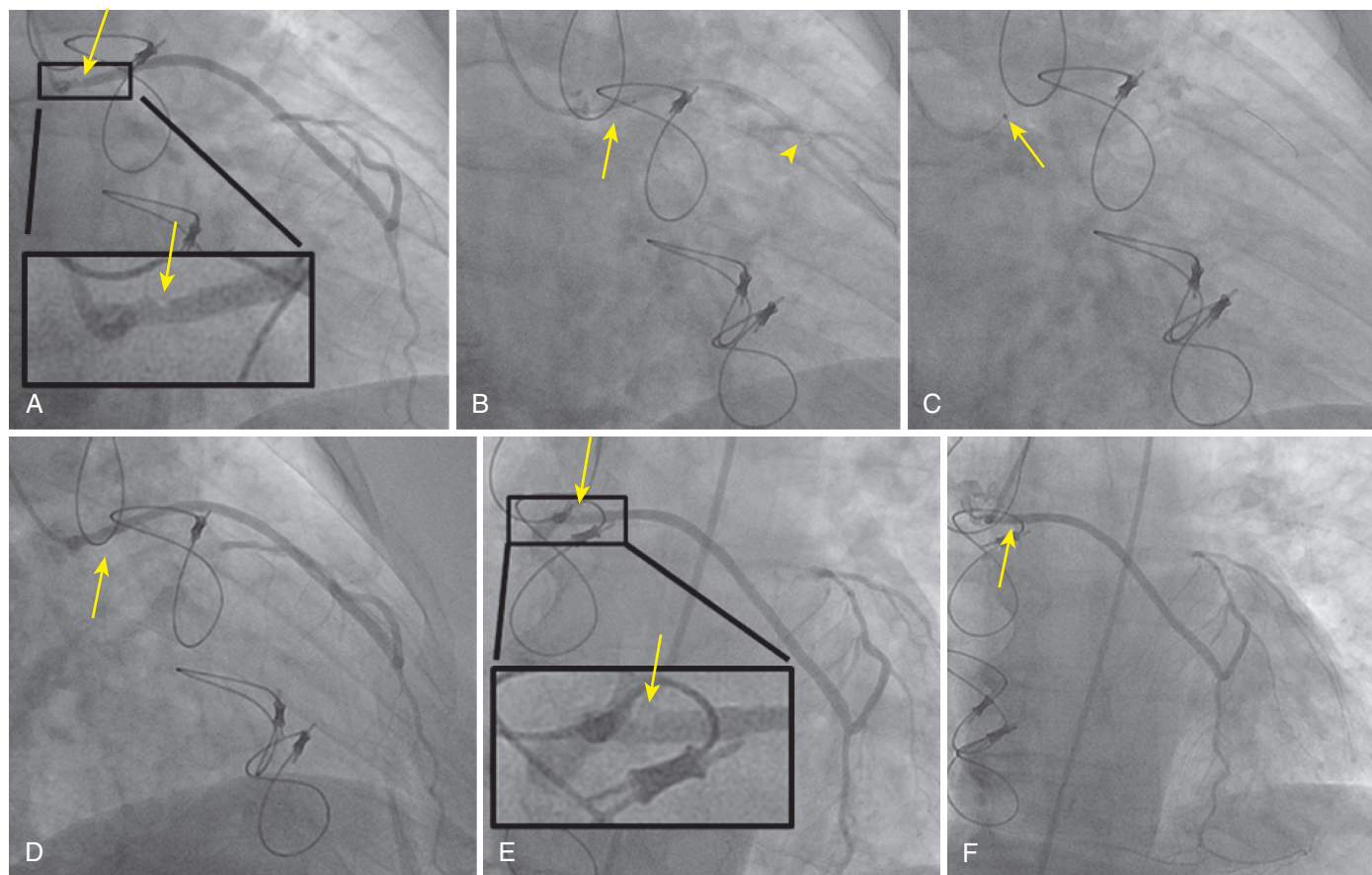


FIGURE 11.10 Complicated treatment of an ostial saphenous vein graft (SVG) lesion using an embolic protection device. Coronary angiography demonstrating an ostial lesion in a SVG to the left anterior descending artery (arrow, **A**) that was successfully treated with a implantation of a 3.5- $\times$ 15-mm everolimus-eluting stent (arrow, **B**) after inserting a FilterWire (Boston Scientific) (arrowhead, **C**) for distal embolic protection. After stenting, the FilterWire retrieval catheter (arrow, **C**) could not be advanced through the ostial SVG stent, necessitating filter withdrawal through the stent. A satisfactory angiographic result was achieved (arrow, **D**). One hour later, the patient developed chest pain and cardiac arrest. Emergency angiography during cardiopulmonary resuscitation revealed stent thrombosis of the ostial stent (arrow, **E**), which was successfully treated with implantation of two bare-metal stents (3 $\times$ 28 mm and 3.5 $\times$ 28 mm) (arrow, **F**). (Reproduced with permission from Abdel-Karim AR, Papayannis AC, Mahmood A, et al. Role of embolic protection devices in ostial saphenous vein graft lesions. *Catheter Cardiovasc Interv.* 2012;80:1120-1126.)

ostial SVG lesions were excluded from the pivotal SVG PCI trials, a study showed high success rates with EPD use in ostial lesions at the cost of difficulty retrieving the filter in 11% of the lesions³⁰; one of these patients developed acute stent thrombosis, causing cardiac arrest³⁰ (Figure 11.10). Moreover, ostial and distal anastomotic lesions are more likely to consist of fibrous tissue and less likely to contain lipid core plaque compared with SVG shaft lesions and hence may be less likely to embolize.³⁸ Distal anastomotic lesions (see Figure 11.9) cannot be protected with any of the currently available EPDs. Distal anastomotic lesions constitute approximately 19% of SVG lesions undergoing PCI.⁷ Routine use of EPDs in SVG in lesions caused by in-stent restenosis may be unnecessary (i.e., these lesions are usually caused by neointimal proliferation, making distal embolization unlikely).³⁹ Similarly, EPD use may not be necessary for recently implanted (<2 years old) SVGs that have not had enough time to develop significant degeneration, predisposing to embolization. When EPD delivery is challenging, predilatation with a small balloon or use of a buddy wire can be used to facilitate delivery,⁴⁰ but the buddy wire should be removed before stenting to prevent inadvertent stenting of the buddy wire, leading to EPD entrapment.⁴¹

The 2018 ESC/EACS guidelines on myocardial revascularization¹² downgraded the indication of EPD use in SVG PCI to Class IIa, level of evidence B based on observational studies.⁴²⁻⁴⁴ Observational studies, however, are prone to selection bias and cannot override the results of RCTs.⁴⁵ The 2021 American College of Cardiology Foundation/AHA/Society for Cardiovascular Angiography and Interventions guidelines provide a Class II (level of evidence B) recommendation for use of EPDs in SVG PCI when technically feasible.¹¹ EPDs remain underused in clinical practice: they were used in 21% of the SVG PCIs in the United States between 2005 and 2009,^{42,46} although some studies suggest that up to 77% of SVG lesions are eligible.⁴⁷ In a study from the US Department of Veterans Affairs, EPDs were used in 37.9% of SVG PCIs between 2008 and 2017 with a significant decline over time (from 35% in 2008 to 30% in 2017).⁴⁸

Potential explanations for EPD underuse include lack of reimbursement for EPDs; technical difficulties and lack of familiarity with EPD use⁴⁹; fear of EPD-related complications, such as device entrapment^{50,51} and acute vessel occlusion³⁰; and uncertainty regarding the magnitude of clinical benefit with EPD use. The SAFER trial was performed before the era of potent ADP P2Y₁₂-receptor inhibitors. In the ISAR-CABG (Is Drug-Eluting-Stenting Associated with

Improved Results in Coronary Artery Bypass Grafts?) trial in which all patients were pretreated with 600 mg of clopidogrel before PCI, despite very infrequent EPD use (in <1% of SVG PCIs), the incidence of MI was 6%, which is lower than the incidence of MI reported in the control arm of the SAFER trial (14.7%).³²

When use of an EPD is not feasible (e.g., in distal anastomotic lesions, lesions without an adequate landing zone, tight lesions that cannot be crossed with an EPD, or thrombotic lesions in which EPD insertion may cause embolization by itself) (see Figure 11.9), alternative interventions to reduce distal embolization (or obviate its adverse consequences) include (1) intragraft vasodilator administration (e.g., adenosine,⁵² nitroprusside,⁵³ nicardipine,⁵⁴ verapamil⁵⁵), (2) use of an excimer laser,⁵⁶ (3) implantation of slightly undersized stents⁵⁷ (which did not result in higher restenosis rates in one retrospective study⁵⁷), or (4) direct stenting without predilation.^{58,59}

SAPHENOUS VEIN GRAFT STENTING

Bare-metal stents (BMSs) improved the outcomes of balloon angioplasty in SVG lesions,^{60,61} but covered stents did not.⁶²⁻⁶⁵ Drug-eluting stents (DESs) and BMSs provide similar long-term outcomes after SVG stenting (Table 11.3)⁶⁶⁻⁷⁴ as shown by the two largest RCTs published in this field.^{71,74}

The RRISC (Reduction of Restenosis In Saphenous vein grafts with Cypher sirolimus-eluting stent) trial compared the sirolimus-eluting stent (SES) Cypher (Cordis) with a BMS in 75 patients and reported less angiographic restenosis and TLR at 6 months.^{66,67} During long-term follow-up, the SES group had a higher mortality rate (29% vs 0%; $P = .001$), and target vessel revascularization was similar in both groups⁶⁷; however, most patients died because of noncardiac causes or cardiac causes unrelated to the target SVG.

The SOS (Stenting Of Saphenous Vein Grafts) trial compared a paclitaxel-eluting stent (PES), Taxus (Boston Scientific), with a similar BMS in 80 patients and demonstrated less angiographic restenosis and lower incidence of clinical events (both repeat revascularization and MI) with PES.^{68,69}

The ISAR-CABG study randomized 610 patients to a first-generation DES (SES, PES, or sirolimus-eluting ISAR stent) or a BMS. At 12 months, the DES group had significantly lower incidence of TLR (7% vs 13%, $P = .01$) compared with BMS, with a similar incidence of all-cause death (5% vs 5%; $P = .83$), MI (5% vs 6%; $P = .27$), and definite or probable stent thrombosis (1% vs 1%; $P = .99$).⁷⁰ The incidences of occlusive restenosis were 6% with DESs and 12% with BMSs ($P = .008$).⁷⁰ Stent failure in SVG lesions frequently presents with an acute coronary syndrome (ACS).⁷⁵ However, at 5 years, the incidence of major adverse events was similar in the DES and BMS groups.

The DIVA (Drug-Eluting Stents vs Bare-Metal Stents in Saphenous Vein Graft Angioplasty) trial, which used

TABLE 11.3 Trials of Saphenous Vein Graft Lesion Stenting

AUTHOR	YEAR	PATIENTS (n)	PRIMARY ENDPOINT	BARE METAL STENT EVENT RATE (%)	OTHER GROUP EVENT RATE (%)	P VALUE
BMS vs balloon angioplasty						
SAVED ⁶⁰	1997	220	6-mo angiographic restenosis	37	46	.24
Venestent ⁶¹	2003	150	6-mo angiographic restenosis	19.1	32.8	.069
BMS vs covered stents						
RECOVERS ⁶²	2003	301	6-mo angiographic restenosis	24.8	24.2	.237
STING ⁶³	2003	211	6-mo angiographic restenosis	20	29	.15
SYMBIOT III ⁶⁴	2006	700	8-mo angiographic percent diameter stenosis	30.9	31.9	.80
BARRICADE ⁶⁵	2011	243	8-mo angiographic restenosis	28.4	31.8	.63
BMS vs DES						
RRISC ⁶⁶	2006	75	6-mo angiographic restenosis	32.6	13.6	.031
RRISC ⁶⁷	2007		MACE at 32 mo	41	58	.13
SOS ⁶⁸	2009	80	12-mo angiographic restenosis	51	9	< .001
SOS ⁶⁹	2010	80	TVF at 35 mo	72	34	.001
ISAR-CABG ⁷⁰	2011	610	12-mo composite of death, MI, and TLR	22	15	.02
ISAR-CABG ⁷¹	2018		60-mo composite of cardiac death, MI, and TVR	54	56	.89
ADEPT ⁷²	2018	57	Late lumen loss at 6 mo	0.47 ± 0.95 mm	0.53 ± 1.09 mm	.86
DIVA ⁷³	2018	597	Composite of cardiac death, target vessel MI, and TVR during median follow-up of 2.7 y	34	37	.44
BASKET-SAVAGE ⁷⁴	2020	173	60-mo composite of cardiac death, MI, and TVR	56	36	< .001

ADEPT, Comparison between the STENTYS self-apposing bare metal and paclitaxel-eluting coronary stents for the treatment of saphenous vein grafts; BARRICADE, Barrier Approach to Restenosis: Restrict Intima to Curtail Adverse Events Trial; BASKET-SAVAGE, Study to Test the Efficacy and Safety of Drug Eluting vs. Bare-Metal Stents for Saphenous Vein Graft Interventions; BMS, bare-metal stent; DES, drug-eluting stent; DIVA, Drug-Eluting Stents vs Bare-Metal Stents in Saphenous Vein Graft Angioplasty; ISAR-CABG, Is Drug-Eluting-Stenting Associated with Improved Results in Coronary Artery Bypass Grafts? Trial; MACE, major adverse cardiac event; MI, myocardial infarction; RECOVERS, European multicenter Randomized Evaluation of polytetrafluoroethylene COVERed stent in Saphenous vein grafts Trial; RRISC, Reduction of Restenosis In Saphenous vein grafts with Cypher sirolimus-eluting stent Trial; SAVED, Saphenous Vein De Novo Trial; SOS, Stenting Of Saphenous vein grafts Trial; STING, Stents IN Grafts Trial; SYMBIOT III, A Prospective, Randomized Trial of a Self-Expanding PTFE Stent Graft During SVG Intervention; TLR, target lesion revascularization; TVF, target vessel failure.



contemporary second-generation DESs in most (88%) patients randomized to DES, reported no benefit with DESs over BMSs on target vessel failure rates (37% vs 34%; $P = .44$) during a mean follow-up of 2.7 years.⁷³

A meta-analysis of six RCTs showed similar cardiovascular mortality rate (1.00 [0.64–1.57]; $P = .99$), all-cause mortality rate (1.11 [0.77–1.62]; $P = .57$), rate of MI (0.74 [0.48–1.16]; $P = .19$), stent thrombosis (1.06 [0.42–2.65]; $P = .90$), and TVR (0.73 [0.48–1.11]; $P = .14$) in patients who received DESs versus BMSs in SVG lesions.⁷⁶

ADJUNCTIVE PHARMACOTHERAPY

Anticoagulation for SVG PCI can be achieved with unfractionated heparin or bivalirudin. Glycoprotein (GP) IIb/IIIa inhibitors are not beneficial⁷⁷ and may be harmful⁷⁸ in SVG PCI (Class III, level of evidence B ACC/AHA guideline recommendation).¹¹ However, GP IIb/IIIa inhibitors were used in 40% of SVG PCI in the United States in the NCDR between 2004 and 2009.⁷⁹

Prehospital administration of single or dual oral antiplatelet therapy has been associated with better outcomes after SVG PCI compared with no prehospital therapy.⁸⁰ After SVG PCI with DES, 12-month duration of dual antiplatelet therapy (DAPT) remains the standard of care; however, high rates of death and MI were observed after clopidogrel discontinuation at 12 months in one study,⁸¹ suggesting that prolonged DAPT might be advantageous. Patients who undergo SVG PCI and have high platelet reactivity have high 2-year rates of major adverse cardiac events.⁸² Moreover, the SVG target vessel is one of the determinants of the DAPT score: it provides 2 points, and a DAPT score of 2 or greater is associated with a favorable benefit-to-risk ratio for more than the 12-month duration of DAPT.⁸³ Optimizing the overall medical regimen and aggressively controlling coronary artery disease risk factors are important, given the high risk profile and poor risk factor control of patients undergoing SVG PCI.²⁷

TECHNICAL ASPECTS OF SAPHENOUS VEIN GRAFT PERCUTANEOUS CORONARY INTERVENTION: INTRAVASCULAR IMAGING

Intravascular imaging (see [Figure 11.4](#)) can facilitate SVG PCI by optimal stent size selection and evaluation of the need for pretreatment, for example, in SVGs containing thrombus.²⁸ Stent undersizing in SVG PCI could result in stent deformation when equipment is advanced through the stent.⁸⁴ In a preliminary study, slight undersizing of SVG stents and avoiding postdilation were associated with lower risk of distal embolization.⁵⁷ Intravascular imaging can facilitate detection and treatment of heavily calcified balloon undilatable SVG lesions, some of which may require advanced calcium modification strategies, such as atherectomy⁸⁵ or intravascular lithotripsy.⁸⁶ Intravascular imaging can help determine the cause of in-stent restenosis: intravascular ultrasonography of 54 restenotic SVG lesions revealed a mechanical cause in 33% of cases (stent underexpansion in 10 cases, 6 stent fracture or deformation in 6, and uncovered aorto-anastomotic lesions in 2).⁸⁷

SAPHENOUS VEIN GRAFT ENGAGEMENT

Bypass graft engagement is significantly facilitated when the CABG anatomy is known⁸⁸; hence, every effort should be made to obtain the CABG surgical report before angiography. When such a report cannot be obtained, a systematic approach should be followed with nonselective injections of both subclavian arteries (to identify any IMA grafts) and ensuring that the perfusion of each myocardial segment is accounted for. SVG engagement is easier when graft markers are present ([Figure 11.11](#)), yet such markers are very infrequently inserted at the time of CABG, in part because of concerns on their effect on SVG patency.⁸⁹

The usual location of the SVG proximal anastomosis is shown in [Figure 11.12](#). SVGs to the right coronary artery or the right posterior descending artery usually arise from the right side of the aorta. SVGs to the left coronary artery arise from the left side of the aorta: SVGs to the left anterior descending artery originate lower, SVGs to the diagonal originate higher, and SVGs to the obtuse marginal branches originate even higher in the aorta. A JR4 or 3DRC catheter can usually engage most left- and right-sided grafts. A multipurpose catheter can facilitate cannulation of SVGs to the right coronary/posterior descending artery and an LCB (Left Coronary Bypass) catheter cannulation of left-sided grafts.

Engagement of arterial and SVGs can be performed using either a femoral or a radial approach. In the RADIAL-CABG (Randomized Comparison of the Transradial and Transfemoral Approaches for Coronary Artery Bypass Graft Angiography and Intervention) clinical trial, coronary artery and graft angiography was faster and required less contrast and radiation exposure for both the patient and operator when performed using femoral compared with radial access, and the crossover rate from radial to femoral was 17.2%.⁹⁰ In contrast, the L-RECORD (Left Radial Compared to Femoral Approach for Coronary Angiography in Patients with Previous CABG) trial showed similar procedure and fluoroscopy time and contrast volume with 2.7% crossover from radial to femoral access.⁹¹

If radial access is selected, the left radial artery should be used in most cases to facilitate engagement of the left internal mammary artery (LIMA) and the other bypass grafts.⁹² If use of the left radial artery is not feasible, the right radial artery can be used, but LIMA engagement can be challenging. Use of a JL 4, a Simmons catheter, or a Bartorelli-Cozzi catheter can facilitate LIMA engagement through right radial access. Graft engagement and PCI can be facilitated by guide catheter extensions,^{93,94} but these may cause ostial dissections. When graft engagement is challenging via radial access, early conversion to femoral access should be considered.⁹⁵ In patients with bilateral IMA grafts, upfront femoral access is preferred.

ACUTELY OCCLUDED SAPHENOUS VEIN GRAFTS

Acutely occluded SVGs may contain a large amount of thrombus, and even when they are successfully recanalized, they are at high risk for recurrent failure.⁹⁶ Treatment options have included combined use of thrombectomy

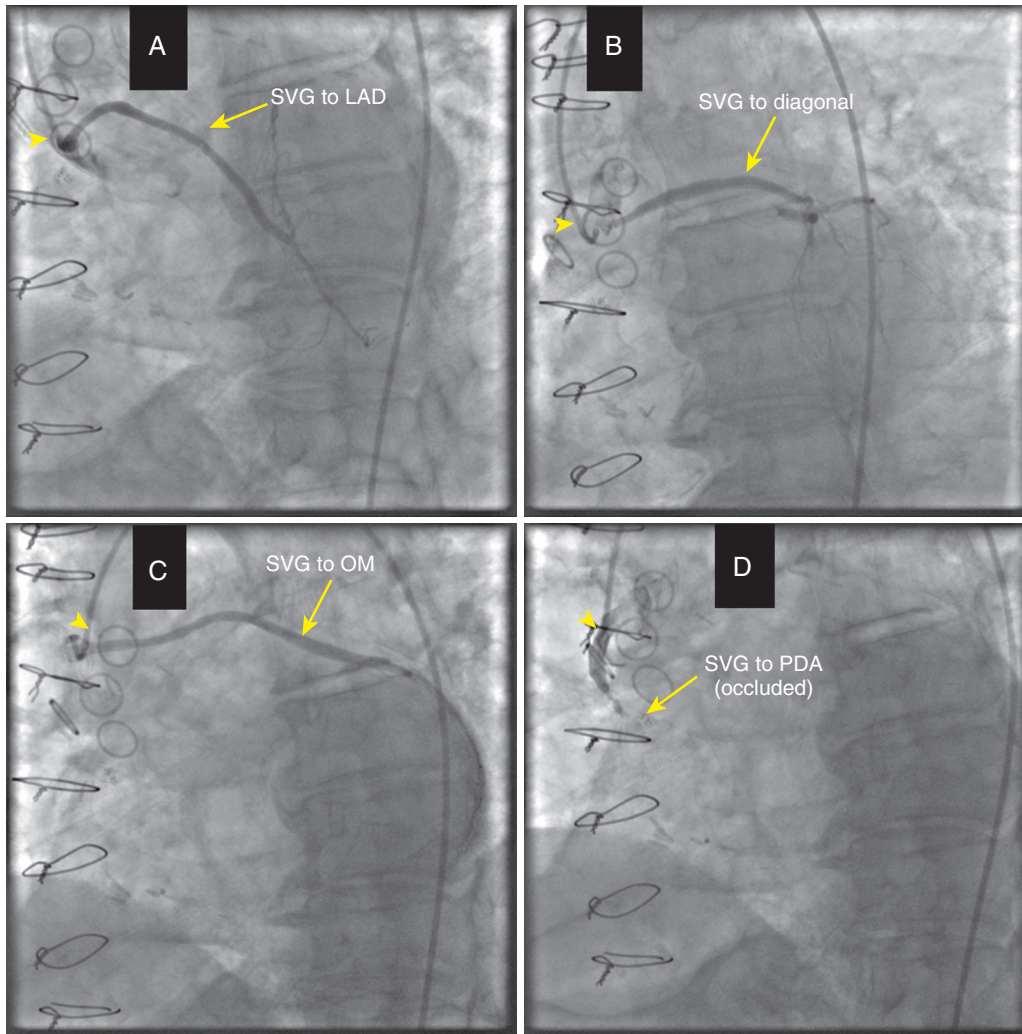


FIGURE 11.11 Example of a patient with bypass graft markers facilitating saphenous vein graft (SVG) engagement. The *lower left-sided marker* marks the ostium of a SVG to the left anterior descending coronary artery (LAD) (**A**), the *mid left-sided marker* marks the ostium of a SVG to a diagonal branch (**B**), and the *higher left-sided marker* marks the ostium of a SVG to an obtuse marginal (OM) branch (**C**). The *right-sided marker* marks the ostium of the SVG to the posterior descending artery (PDA) (this graft is occluded, *arrow*, **D**). RCA, Right coronary artery.

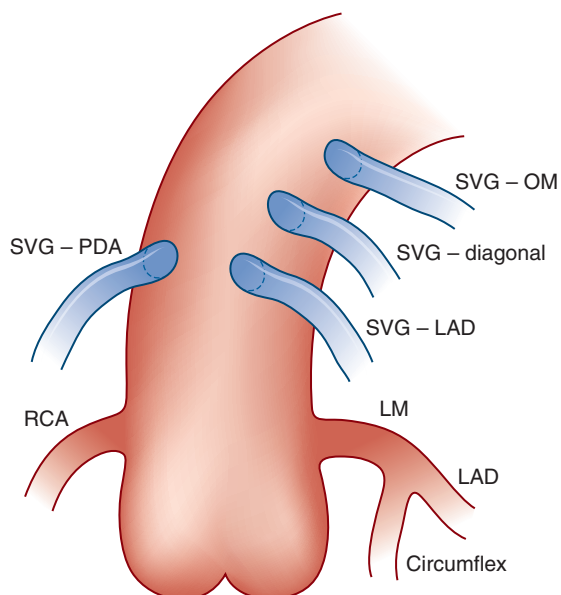


FIGURE 11.12 Usual location of the saphenous vein graft (SVG) proximal anastomoses. LAD, Left anterior descending artery; LM, left main; OM, obtuse marginal; PDA, posterior descending artery; RCA, right coronary artery.

and an EPD⁹⁷ as well as laser.⁹⁸ Thrombectomy can sometimes be performed by deep SVG intubation with a guide catheter⁹⁹ (Figure 11.13) or with a guide catheter extension. If thrombectomy fails, dilatation with an undersized balloon can be performed to restore TIMI (Thrombolysis In Myocardial Infarction) 1 to 2 flow followed by anticoagulation for 1 to 2 weeks before proceeding with stent implantation.¹⁰⁰ Alternatively, native coronary artery PCI can be performed instead of SVG PCI, if feasible²⁰ (Figure 11.14).

CHRONICALLY OCCLUDED SAPHENOUS VEIN GRAFTS

Percutaneous coronary intervention of SVG CTOs was given a Class III recommendation (level of evidence C) in the 2011 PCI guidelines¹¹ because of relatively low success and high restenosis rates.^{101,102} SVG CTO PCI is currently reserved for cases in which native vessel PCI cannot be accomplished and can provide significant symptomatic improvement.^{103,104}

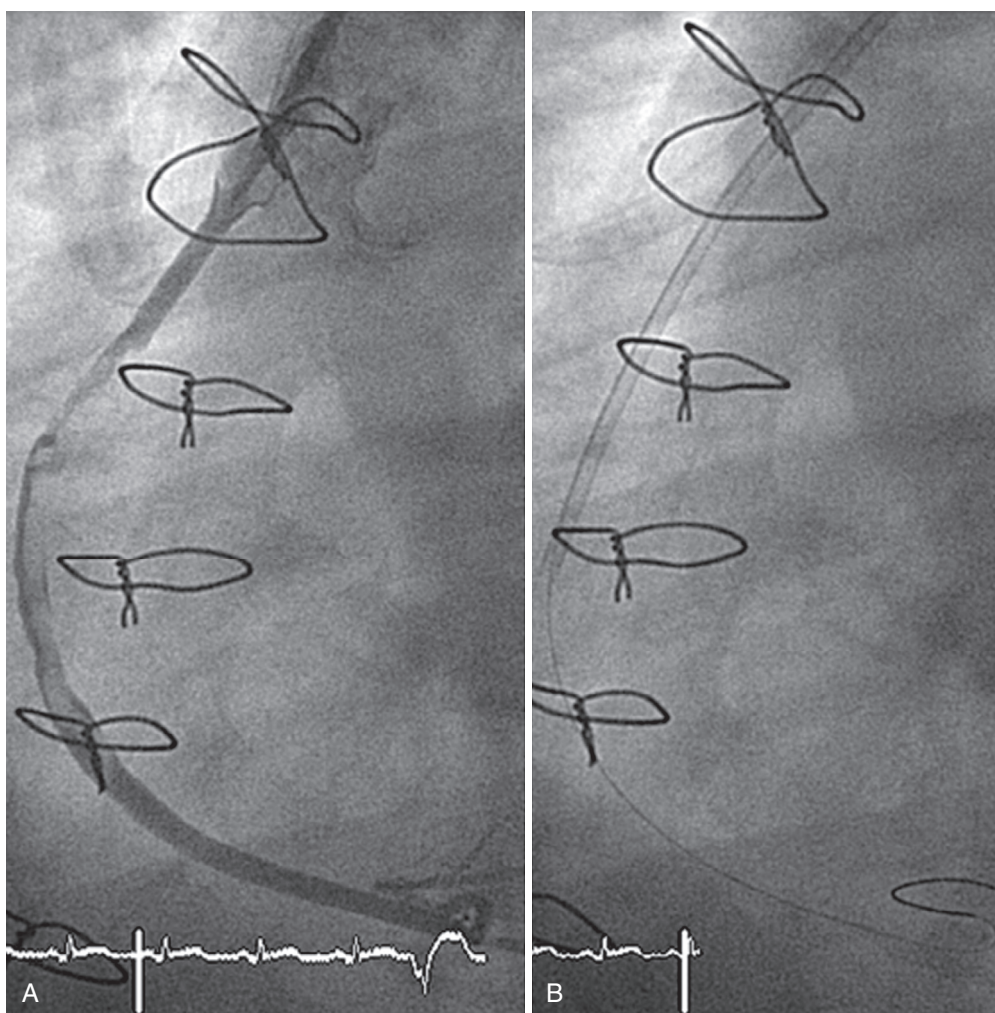


FIGURE 11.13 A and B, Saphenous vein graft thrombectomy using deep guide intubation. The guide catheter is advanced to the middle of the saphenous vein graft in panel B. (Reproduced with permission from Garcia-Tejada J, Jurado-Roman A, Hernandez F, et al. Guiding-catheter thrombectomy combined with distal protection during primary percutaneous coronary intervention of a saphenous vein graft. *Cardiovasc Revasc Med.* 2013;14:356-358.)

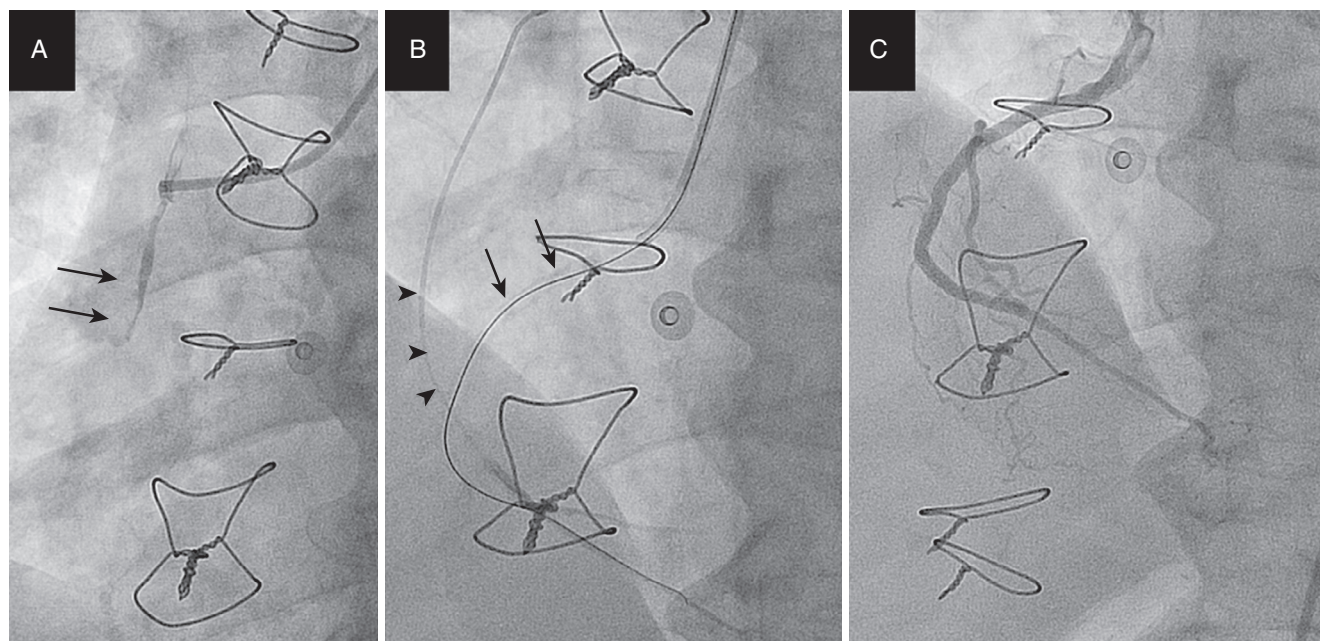


FIGURE 11.14 Treatment of native coronary artery chronic total occlusion after failure to recanalize an acutely occluded saphenous vein graft (SVG). Coronary angiography demonstrates acute thrombotic occlusion of a SVG to the right posterior descending artery (arrow, **A**). After attempts to intervene on the SVG failed, the native right coronary artery chronic total occlusion was successfully crossed (arrows, **B**) with visualization via contrast injection through a microcatheter inserted through the occluded SVG (arrowheads, **B**). After stenting of the native right coronary artery, TIMI (Thrombolysis In Myocardial Infarction) 3 flow to the right posterior descending artery was restored (**C**). (Reproduced with permission from Abdel-Karim AR, Banerjee S, Brilakis ES. Percutaneous intervention of acutely occluded saphenous vein grafts: contemporary techniques and outcomes. *J Invasive Cardiol.* 2010;22:253-257.)

INTERMEDIATE SAPHENOUS VEIN GRAFT LESIONS

Unlike intermediate lesions in native coronary arteries, which have low rates of progression, intermediate lesions in SVG can progress rapidly, often causing ACSs¹⁰⁵⁻¹⁰⁸ (Figure 11.15). Hence, physiologic assessment has a limited role in intermediate SVG lesions.^{108,109} In the VELETI (Moderate VEin Graft LEsion Stenting With the Taxus Stent and Intravascular Ultrasound) pilot trial, patients who underwent intermediate SVG lesion stenting with a PES had a lower rate of SVG disease progression and a trend toward a lower incidence of major adverse cardiac events (MACEs) at 1-year follow-up compared with medical treatment alone.¹⁰⁶ Over a 5-year period, MACE related to the target SVG lesion tended to be lower in the PES group (17% vs 33%; $P = .146$) because of a lower lesion revascularization rate (13% vs 33%; $P = .072$).¹¹⁰ However, in the larger VELETI II trial, which enrolled 125 patients during a median follow-up period of 3.4 years, the incidence of MACEs related to the target SVG lesion was not significantly different among patients who received a DES and those who were treated medically (10% vs 17%; $P = .21$). As a result, prophylactic stenting of intermediate SVG lesions is not currently recommended.

SAPHENOUS VEIN GRAFT PERCUTANEOUS CORONARY INTERVENTION COMPLICATIONS

Apart from distal embolization and no reflow, SVG PCI can result to complications similar to those of non-SVG PCI.

Saphenous vein graft PCI carries increased risk of coronary perforation (Figure 11.16).¹¹¹ Although overall the outcomes of coronary perforation are better in prior CABG patients,¹¹¹ they can sometimes lead to loculated hematomas, resulting in cardiac chamber compromise and hemodynamic collapse (dry tamponade).¹¹² Such loculated effusions may require surgery or computed tomography-guided drainage for treatment. Prompt identification and treatment of coronary or graft perforation is therefore critical in prior CABG patients.^{113,114} Occasionally, SVG perforation

can cause hemoptysis, likely because of the proximity of the SVG with the lung parenchyma.¹¹⁵ Perforated SVGs are at high risk for subsequent occlusion.¹¹⁶

ARTERIAL GRAFT INTERVENTIONS

As described earlier in this chapter, PCI of arterial grafts is significantly less frequent than SVG interventions.⁶ PCI of IMA grafts carries higher risk of dissection but is associated with more favorable follow-up outcomes than SVG PCI.¹¹⁷ PCI of IMA grafts is most commonly needed at the distal anastomotic site and can be hindered by (1) difficulty engaging the graft, especially in the presence of proximal subclavian artery tortuosity; (2) difficulty wiring and delivering equipment through the graft due to “pseudolesion” formation; and (3) difficulty reaching the target lesion because of long graft length. Specialized catheters have been developed to facilitate IMA engagement (e.g., the IM VB1 catheter), yet in cases of severe subclavian tortuosity, ipsilateral radial access may be required to achieve IMA engagement. Care should be used when engaging the IMA ostium to prevent injury. Using soft guidewires may decrease the risk for IMA pseudolesion formation,¹¹⁸ and occasionally, the use of shortened guide catheters may be needed to allow balloon or stent delivery to a distal anastomotic lesion (Figure 11.17) or to a lesion in the native vessel distal to the IMA anastomosis. In patients with in situ IMA grafts, the proximal subclavian artery should be imaged during diagnostic angiography because severe proximal subclavian stenosis can present with angina (caused by subclavian steal syndrome; Figure 11.18 and Video 11.5) and even with MI.¹¹⁹

COMPLICATIONS OF PERCUTANEOUS CORONARY INTERVENTION IN PRIOR CORONARY ARTERY BYPASS GRAFTING PATIENTS

Because of higher anatomic complexity and more comorbidities, PCI in prior CABG patients is associated with an increased risk of complications.

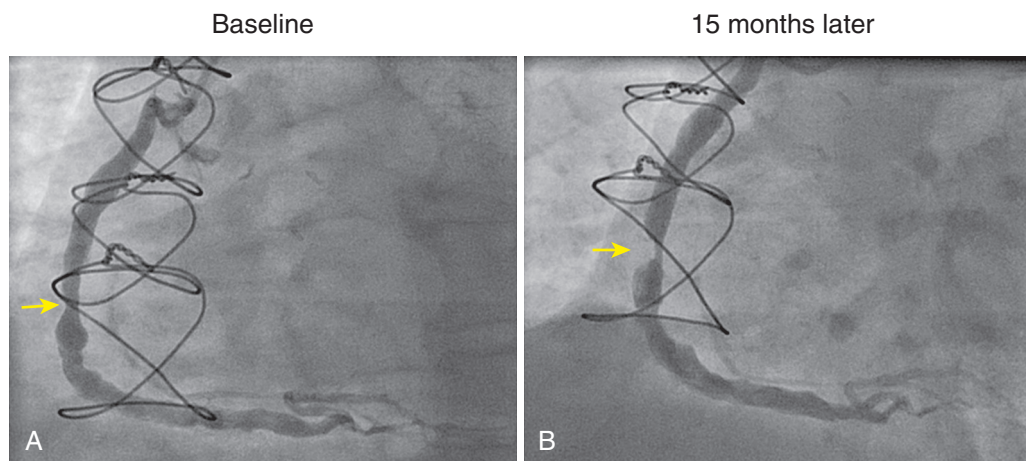


FIGURE 11.15 Rapid progression of an intermediate saphenous vein graft lesion (arrows). **A**, Baseline. **B**, Fifteen months later. (Reproduced with permission from Abdel-Karim AR, Da Silva M, Lichtenwalter C, et al. Prevalence and outcomes of intermediate saphenous vein graft lesions: findings from the stenting of saphenous vein grafts randomized-controlled trial. *Int J Cardiol*. 2013;168:2468-2473.)

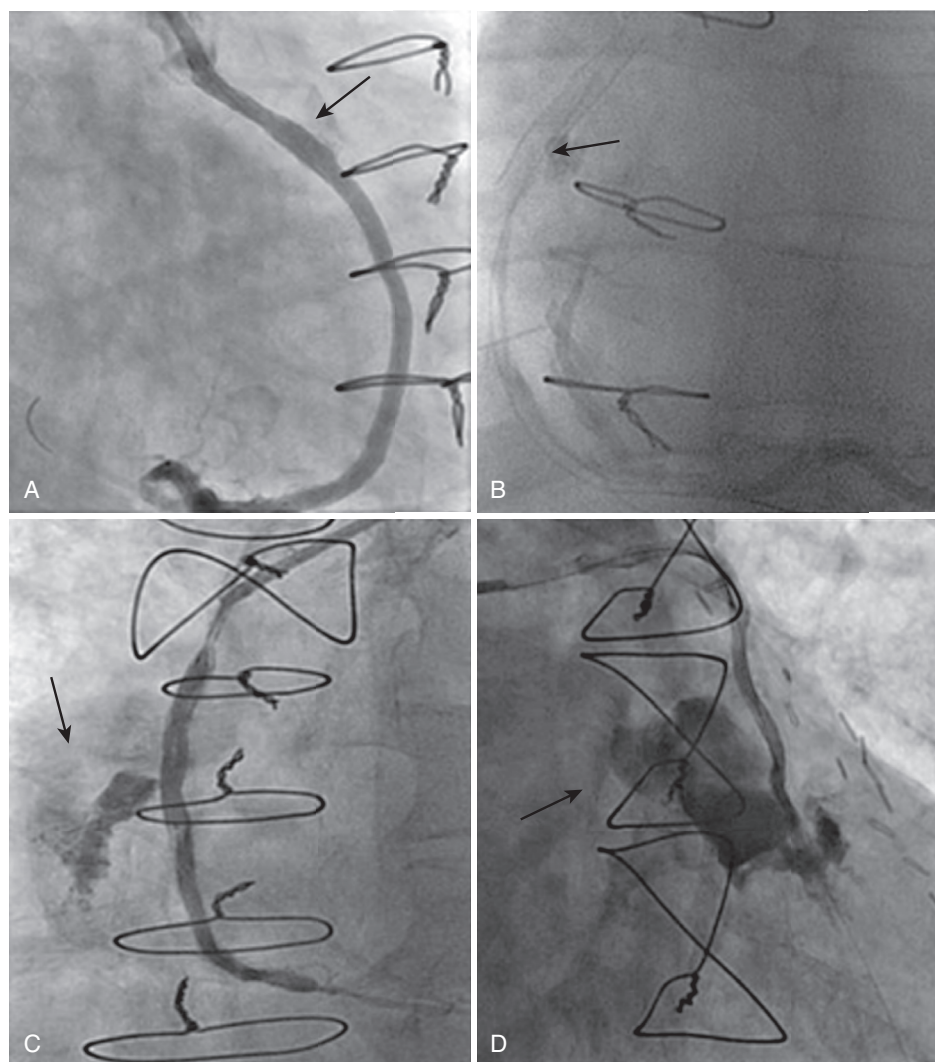


FIGURE 11.16 Examples of a saphenous vein graft perforation. **A**, Class I perforation after balloon angioplasty. **B**, Class II perforation after stent placement. **C**, Class III perforation after postdilatation. **D**, Class III perforation with cavity spilling. (Reproduced with permission from Marmagkiolis K, Brilakis ES, Hakeem A, Cilingiroglu M, Bilodeau L. Saphenous vein graft perforation during percutaneous coronary intervention: a case series. *J Invasive Cardiol.* 2013;25:157-161.)

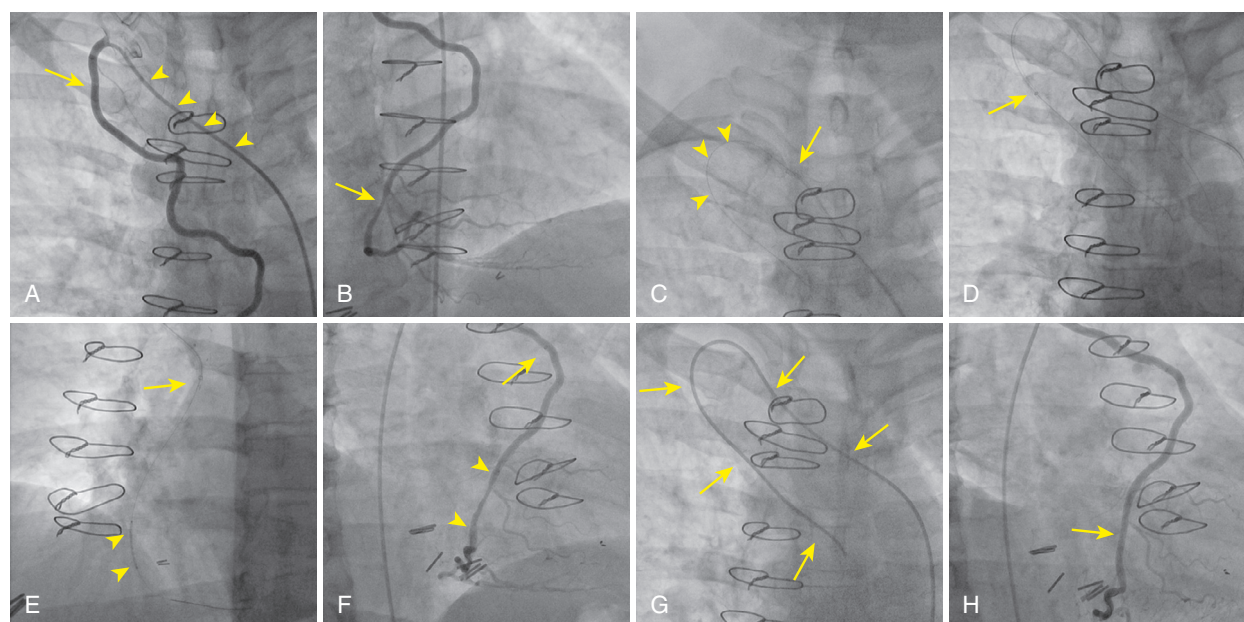


FIGURE 11.17 Treatment of an internal mammary artery distal anastomotic lesion. Diagnostic coronary angiography of the right internal mammary artery (arrowheads, **A**) via a 3DRC diagnostic catheter (arrow, **A**) demonstrates a distal anastomotic lesion (arrow, **B**). The 3DRC diagnostic catheter was removed (arrow, **C**) over a Grand Slam (Abbott Vascular) guidewire (arrowheads, **C**), and a Proxis catheter (St. Jude Medical) (arrow, **D**) was inserted into the right internal mammary artery over the guidewire without using a guide catheter. Injection of contrast via a deep-seated Proxis catheter (arrow, **E-G**) allowed positioning of a 3.0- × 23-mm sirolimus-eluting stent (arrowheads, **E** and **F**) across the distal anastomotic lesion with resolution of the lesion in poststenting angiography (**H**). (Reproduced with permission from Brilakis ES, Banerjee S. Novel uses of the Proxis embolic protection catheter. *Catheter Cardiovasc Interv.* 2009;74:438-445.)¹²⁰

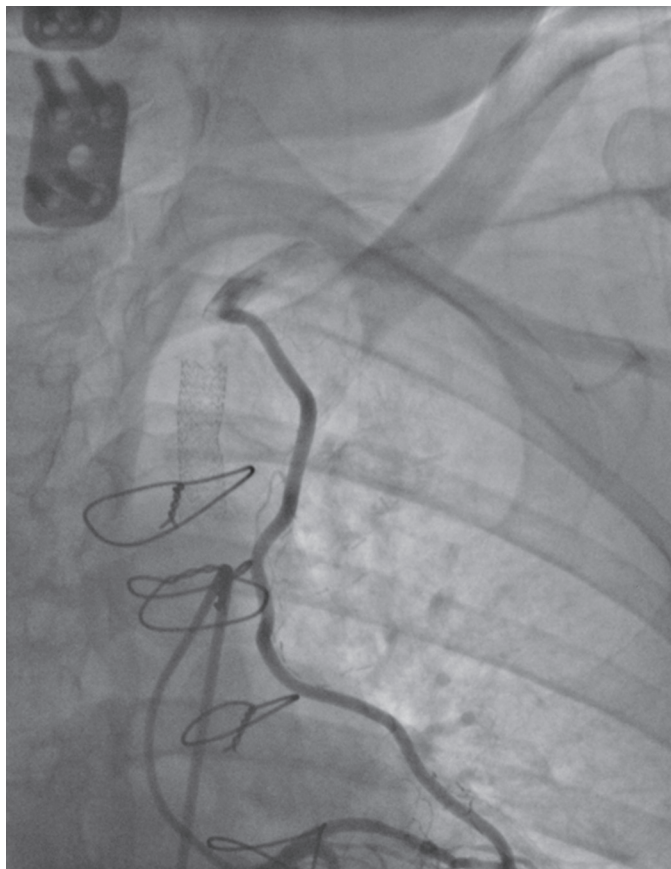


FIGURE 11.18 Example of subclavian steal syndrome. Reversal of flow in the left internal mammary artery graft caused by severe proximal left subclavian stenosis (Video 11.5).

In summary, bypass graft PCI currently accounts for 6.6% of all PCIs. SVG PCI carries increased risk for distal embolization and subsequent SVG failure compared with native coronary artery PCI. EPDs should be used to prevent distal embolization during SVG PCI when technically feasible. DESs should be used in SVG PCI if the patients do not have contraindications to long-term antiplatelet therapy. Native coronary arteries should be preferentially treated instead of bypass graft lesions when technically feasible.

REFERENCES

- Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *N Engl J Med*. 1986;314:1-6.
- Goldman S, Zadina K, Moritz T, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery Results from a Department of Veterans Affairs Cooperative Study. *J Am Coll Cardiol*. 2004;44:2149-2156.
- Widimsky P, Straka Z, Stros P, et al. One-year coronary bypass graft patency: a randomized comparison between off-pump and on-pump surgery angiographic results of the PRAGUE-4 trial. *Circulation*. 2004;110:3418-3423.
- Alexander JH, Hafley G, Harrington RA, et al. Efficacy and safety of edofyllide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. *JAMA*. 2005;294:2446-2454.
- Morice MC, Feldman TE, Mack MJ, et al. Angiographic outcomes following stenting or coronary artery bypass surgery of the left main coronary artery: fifteen-month outcomes from the synergy between PCI with TAXUS express and cardiac surgery left main angiographic substudy (SYNTAX-LE MANS). *EuroIntervention*. 2011;7:670-679.
- Brilakis ES, Rao SV, Banerjee S, et al. Percutaneous coronary intervention in native arteries versus bypass grafts in prior coronary artery bypass grafting patients a report from the national cardiovascular data registry. *JACC Cardiovasc Interv*. 2011;4:844-850.
- Dehmer GJ, Weaver D, Roe MT, et al. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the United States: a report from the CathPCI Registry of the National Cardiovascular Data Registry, 2010 through June 2011. *J Am Coll Cardiol*. 2012;60:2017-2031.
- Yau TM, Borger MA, Weisel RD, Ivanov J. The changing pattern of reoperative coronary surgery: trends in 1230 consecutive reoperations. *J Thorac Cardiovasc Surg*. 2000;120:156-163.
- Yap CH, Sposato L, Akowuah E, et al. Contemporary results show repeat coronary artery bypass grafting remains a risk factor for operative mortality. *Ann Thorac Surg*. 2009;87:1386-1391.
- Morrison DA, Sethi G, Sacks J, et al. Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. *J Am Coll Cardiol*. 2002;40:1951-1954.
- Lawton J, Tamis-Holland J, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization. *J Am Coll Cardiol*. 2022 Jan;79(2):e21-e129. <https://doi.org/10.1016/j.jacc.2021.09.006>.
- Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
- Varghese I, Samuel J, Banerjee S, Brilakis ES. Comparison of percutaneous coronary intervention in native coronary arteries vs. bypass grafts in patients with prior coronary artery bypass graft surgery. *Cardiovasc Revasc Med*. 2009;10:103-109.
- Bundhoo SS, Kalla M, Anantharaman R, et al. Outcomes following PCI in patients with previous CABG: a multi centre experience. *Catheter Cardiovasc Interv*. 2011;78:169-176.
- Xanthopoulos I, Davlouros P, Tsigkas G, Panagiotou A, Hahalis G, Alexopoulos D. Long-term clinical outcome after percutaneous coronary intervention in grafts vs native vessels in patients with previous coronary artery bypass grafting. *Can J Cardiol*. 2011;27:716-724.
- Brilakis ES, O'Donnell CI, Penny W, et al. Percutaneous coronary intervention in native coronary arteries versus bypass grafts in patients with prior coronary artery bypass graft surgery: insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. *JACC Cardiovasc Interv*. 2016;9:884-893.
- Michael TT, Karpaliotis D, Brilakis ES, et al. Impact of prior coronary artery bypass graft surgery on chronic total occlusion revascularisation: insights from a multicentre US registry. *Heart*. 2013;99:1515-1518.
- Xenogiannis I, Tajti P, Hall AB, et al. Update on cardiac catheterization in patients with prior coronary artery bypass graft surgery. *JACC Cardiovasc Interv*. 2019;12:1635-1649.
- Xenogiannis I, Tajti P, Burke MN, Brilakis ES. Staged revascularization in patients with acute coronary syndromes due to saphenous vein graft failure and chronic total occlusion of the native vessel: a novel concept. *Catheter Cardiovasc Interv*. 2019;93:440-444.
- Brilakis ES, Banerjee S, Lombardi WL. Retrograde recanalization of native coronary artery chronic occlusions via acutely occluded vein grafts. *Catheter Cardiovasc Interv*. 2010;75:109-113.
- Dautov R, Manh Nguyen C, Altisent O, Gibrat C, Rinfret S. Recanalization of chronic total occlusions in patients with previous coronary bypass surgery and consideration of retrograde access via saphenous vein grafts. *Circ Cardiovasc Interv*. 2016;9:e003515.
- Xenogiannis I, Gkargkoula F, Karpaliotis D, et al. Retrograde chronic total occlusion percutaneous coronary intervention via saphenous vein graft. *JACC Cardiovasc Interv*. 2020;13:517-526.
- Wilson SJ, Hanratty CG, Spence MS, et al. Saphenous vein graft sacrifice following native vessel PCI is safe and associated with favourable longer-term outcomes. *Cardiovasc Revasc Med*. 2019;20:1048-1052.
- Jurado-Roman A, Rumoroso JR, Abellan-Huerta J, Lopez-Lliva MT, Sanchez-Perez I, Ruiz-Poveda FL. Coronary artery tenting after bypass grafting: a key issue during percutaneous coronary intervention of a chronic total occlusion. *J Invasive Cardiol*. 2019;31:E2-E3.
- Walters D, Patel M, Penny W. Saphenous vein graft aneurysm: a case-based review of percutaneous management. *Cardiovasc Revasc Med*. 2019;20:1190-1195.
- Katoh H, Nozue T, Michishita I. A case of giant saphenous vein graft aneurysm successfully treated with catheter intervention. *Catheter Cardiovasc Interv*. 2016;87:83-89.
- Boatman DM, Saeed B, Varghese I, et al. Prior coronary artery bypass graft surgery patients undergoing diagnostic coronary angiography have multiple uncontrolled coronary artery disease risk factors and high risk for cardiovascular events. *Heart Vessels*. 2009;24:241-246.
- Davlouros P, Damelou A, Karantalis V, et al. Evaluation of culprit saphenous vein graft lesions with optical coherence tomography in patients with acute coronary syndromes. *JACC Cardiovasc Interv*. 2011;4:683-693.
- Kobayashi T, Higuchi Y, Komatsu S, Yutani C, Hirayama A, Kodama K. Visualization of cholesterol crystals liberated from a diseased saphenous vein coronary bypass graft. *JACC Cardiovasc Interv*. 2020;13:e105-e106.
- Abdel-Karim AR, Papayannis AC, Mahmood A, et al. Role of embolic protection devices in ostial saphenous vein graft lesions. *Catheter Cardiovasc Interv*. 2012;80:1120-1126.
- Hong MK, Mehran R, Dangas G, et al. Creatine kinase-MB enzyme elevation following successful saphenous vein graft intervention is associated with late mortality. *Circulation*. 1999;100:2400-2405.
- Baim DS, Wahr D, George B, et al. Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. *Circulation*. 2002;105:1285-1290.

33. Stone GW, Rogers C, Hermiller J, et al. Randomized comparison of distal protection with a filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of diseased saphenous vein aorto-coronary bypass grafts. *Circulation*. 2003;108:548-553.
34. Carrozza JP Jr, Mumma M, Breall JA, Fernandez A, Heyman E, Metzger C. Randomized evaluation of the TriActiv balloon-protection flush and extraction system for the treatment of saphenous vein graft disease. *J Am Coll Cardiol*. 2005;46:1677-1683.
35. Holmes DR, Coolong A, O'Shaughnessy C, et al. Comparison of the CardioShield filter with the guardwire balloon in the prevention of embolisation during vein graft intervention: results from the CAPTIVE randomised trial. *EuroIntervention*. 2006;2:161-168.
36. Mauri L, Cox D, Hermiller J, et al. The PROXIMAL trial: proximal protection during saphenous vein graft intervention using the Proxis Embolic Protection System: a randomized, prospective, multicenter clinical trial. *J Am Coll Cardiol*. 2007;50:1442-1449.
37. Kereiakes DJ, Turco MA, Breall J, et al. A novel filter-based distal embolic protection device for percutaneous intervention of saphenous vein graft lesions: results of the AMETHYST randomized controlled trial. *JACC Cardiovasc Interv*. 2008;1:248-257.
38. Wood FO, Badhey N, Garcia B, et al. Analysis of saphenous vein graft lesion composition using near-infrared spectroscopy and intravascular ultrasonography with virtual histology. *Atherosclerosis*. 2010;212:528-533.
39. Ashby DT, Dangas G, Aymong EA, et al. Effect of percutaneous coronary interventions for in-stent restenosis in degenerated saphenous vein grafts without distal embolic protection. *J Am Coll Cardiol*. 2003;41:749-752.
40. Kaliyadan AG, Chawla H, Fischman DL, et al. Importance of adjunct delivery techniques to optimize deployment success of distal protection filters during vein graft intervention. *J Invasive Cardiol*. 2017;29:54-58.
41. Brilakis ES. Bypass graft intervention and embolic protection. In: Kern MJ, ed. *SCAI Interventional Cardiology Board Review*. Lippincott Williams & Wilkins; 2014.
42. Brennan JM, Al-Hejily W, Dai D, et al. Three-year outcomes associated with embolic protection in saphenous vein graft intervention: results in 49 325 senior patients in the Medicare-linked National Cardiovascular Data Registry CathPCI Registry. *Circ Cardiovasc Interv*. 2015;8:e001403.
43. Paul TK, Bhatheja S, Panchal HB, et al. Outcomes of saphenous vein graft intervention with and without embolic protection device: a comprehensive review and meta-analysis. *Circ Cardiovasc Interv*. 2017;10:e005538.
44. Shoaib A, Kinnaird T, Curzen N, et al. Outcomes following percutaneous coronary intervention in saphenous vein grafts with and without embolic protection devices. *JACC Cardiovasc Interv*. 2019;12:2286-2295.
45. Brilakis ES, Alaswad K, Burke MN. Embolic protection devices in vein graft interventions: what would you do? *JACC Cardiovasc Interv*. 2019;12:2296-2298.
46. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:e574-e651.
47. Webb LA, Dixon SR, Safian RD, O'Neill WW. Usefulness of embolic protection devices during saphenous vein graft intervention in a nonselected population. *J Interv Cardiol*. 2005;18:73-75.
48. Valle JA, Glorioso TJ, Schuetz KB, Grunwald GK, Armstrong EJ, Waldo SW. Contemporary use of embolic protection devices during saphenous vein graft intervention. *Circ Cardiovasc Interv*. 2019;12:e007636.
49. Mahmood A, Khair T, Abdel-Karim AR, et al. Contemporary approaches to saphenous vein graft interventions: a survey of 275 interventional cardiologists. *Catheter Cardiovasc Interv*. 2012;79:834-842.
50. Badhey N, Lichtenwalter C, de Lemos JA, et al. Contemporary use of embolic protection devices in saphenous vein graft interventions: insights from the stenting of saphenous vein grafts trial. *Catheter Cardiovasc Interv*. 2010;76:263-269.
51. Weinstein RV, Homem Valle F, Pivatto Junior F, et al. Guidewire self-extrusion after entrapment of distal protection device during saphenous vein graft angioplasty. *JACC Cardiovasc Interv*. 2017;10:e3-e5.
52. Sdringola S, Assali A, Ghani M, et al. Adenosine use during aortocoronary vein graft interventions reverses but does not prevent the slow-no reflow phenomenon. *Catheter Cardiovasc Interv*. 2000;51:394-399.
53. Zoghbi GJ, Goyal M, Hage F, et al. Pretreatment with nitroprusside for microcirculatory protection in saphenous vein graft interventions. *J Invasive Cardiol*. 2009;21:34-39.
54. Fischell TA, Subraya RG, Ashraf K, Perry B, Haller S. "Pharmacologic" distal protection using prophylactic, intragraft nicardipine to prevent no-reflow and non-Q-wave myocardial infarction during elective saphenous vein graft intervention. *J Invasive Cardiol*. 2007;19:58-62.
55. Michaels AD, Appleby M, Otten MH, et al. Pretreatment with intragraft verapamil prior to percutaneous coronary intervention of saphenous vein graft lesions: results of the randomized, controlled vasodilator prevention on no-reflow (VAPOR) trial. *J Invasive Cardiol*. 2002;14:299-302.
56. Niccoli G, Belloni F, Cosentino N, et al. Case-control registry of excimer laser coronary angioplasty versus distal protection devices in patients with acute coronary syndromes due to saphenous vein graft disease. *Am J Cardiol*. 2013;112:1586-1591.
57. Hong YJ, Pichard AD, Mintz GS, et al. Outcome of undersized drug-eluting stents for percutaneous coronary intervention of saphenous vein graft lesions. *Am J Cardiol*. 2010;105:179-185.
58. Okabe T, Lindsay J, Torguson R, et al. Can direct stenting in selected saphenous vein graft lesions be considered an alternative to percutaneous intervention with a distal protection device? *Catheter Cardiovasc Interv*. 2008;72:799-803.
59. Latif F, Uyeda L, Edson R, et al. Stent-only versus adjunctive balloon angioplasty approach for saphenous vein graft percutaneous coronary intervention: insights from DIVA trial. *Circ Cardiovasc Interv*. 2020;13:e008494.
60. Savage MP, Douglas JS Jr, Fischman DL, et al. Stent placement compared with balloon angioplasty for obstructed coronary bypass grafts. Saphenous Vein De Novo Trial Investigators. *N Engl J Med*. 1997;337:740-747.
61. Hanekamp CE, Koolen JJ, Den Heijer P, et al. Randomized study to compare balloon angioplasty and elective stent implantation in venous bypass grafts: the Venestent study. *Catheter Cardiovasc Interv*. 2003;60:452-457.
62. Stankovic G, Colombo A, Presbitero P, et al. Randomized evaluation of polytetrafluoroethylene-covered stent in saphenous vein grafts: the Randomized Evaluation of polytetrafluoroethylene COVERED stent in Saphenous vein grafts (RECOVERS) Trial. *Circulation*. 2003;108:37-42.
63. Schachinger V, Hamm CW, Munzel T, et al. A randomized trial of polytetrafluoroethylene-membrane-covered stents compared with conventional stents in aortocoronary saphenous vein grafts. *J Am Coll Cardiol*. 2003;42:1360-1369.
64. Turco MA, Buchbinder M, Popma JJ, et al. Pivotal, randomized U.S. study of the Symbiotrade mark covered stent system in patients with saphenous vein graft disease: eight-month angiographic and clinical results from the Symbiot III trial. *Catheter Cardiovasc Interv*. 2006;68:379-388.
65. Stone GW, Goldberg S, O'Shaughnessy C, et al. 5-year follow-up of polytetrafluoroethylene-covered stents compared with bare-metal stents in aortocoronary saphenous vein grafts the randomized BARRICADE (barrier approach to restenosis: restrict intima to curtail adverse events) trial. *JACC Cardiovasc Interv*. 2011;4:300-309.
66. Vermeersch P, Agostoni P, Verheye S, et al. Randomized double-blind comparison of sirolimus-eluting stent versus bare-metal stent implantation in diseased saphenous vein grafts: six-month angiographic, intravascular ultrasound, and clinical follow-up of the RRISC Trial. *J Am Coll Cardiol*. 2006;48:2423-2431.
67. Vermeersch P, Agostoni P, Verheye S, et al. Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC Trial. *J Am Coll Cardiol*. 2007;50:261-267.
68. Brilakis ES, Lichtenwalter C, de Lemos JA, et al. A randomized controlled trial of a paclitaxel-eluting stent versus a similar bare-metal stent in saphenous vein graft lesions the SOS (Stenting of Saphenous Vein Grafts) trial. *J Am Coll Cardiol*. 2009;53:919-928.
69. Brilakis ES, Lichtenwalter C, Abdel-karim AR, et al. Continued benefit from paclitaxel-eluting compared with bare-metal stent implantation in saphenous vein graft lesions during long-term follow-up of the SOS (Stenting of Saphenous Vein Grafts) trial. *JACC Cardiovasc Interv*. 2011;4:176-182.
70. Mehili J, Pache J, Abdel-Wahab M, et al. Drug-eluting versus bare-metal stents in saphenous vein graft lesions (ISAR-CABG): a randomized controlled superiority trial. *Lancet*. 2011;378:1071-1078.
71. Collieran R, Kufner S, Mehili J, et al. Efficacy over time with drug-eluting stents in saphenous vein graft lesions. *J Am Coll Cardiol*. 2018;71:1973-1982.
72. Ijsselmuiden A, Simsek C, van Driel AG, et al. Comparison between the STENTYS self-apposing bare metal and paclitaxel-eluting coronary stents for the treatment of saphenous vein grafts (ADEPT trial). *Neth Heart J*. 2018;26:94-101.
73. Brilakis ES, Edson R, Bhatt DL, et al. Drug-eluting stents versus bare-metal stents in saphenous vein grafts: a double-blind, randomized trial. *Lancet*. 2018;391:1997-2007.
74. Fahrni G, Farah A, Engstrom T, et al. Long-term results after drug-eluting versus bare-metal stent implantation in saphenous vein grafts: randomized controlled trial. *J Am Heart Assoc*. 2020;9:e017434.
75. Lichtenwalter C, de Lemos JA, Roesle M, et al. Clinical presentation and angiographic characteristics of saphenous vein graft failure after stenting: insights from the SOS (stenting of saphenous vein grafts) trial. *JACC Cardiovasc Interv*. 2009;2:855-860.
76. Patel NJ, Bavishi C, Atti V, et al. Drug-eluting stents versus bare-metal stents in saphenous vein graft intervention. *Circ Cardiovasc Interv*. 2018;11:e007045.
77. Roffi M, Mukherjee D, Chew DP, et al. Lack of benefit from intravenous platelet glycoprotein IIb/IIIa receptor inhibition as adjunctive treatment for percutaneous interventions of aortocoronary bypass grafts: a pooled analysis of five randomized clinical trials. *Circulation*. 2002;106:3063-3067.
78. Coolong A, Baim DS, Kuntz RE, et al. Saphenous vein graft stenting and major adverse cardiac events: a predictive model derived from a pooled analysis of 3958 patients. *Circulation*. 2008;117:790-797.
79. Brilakis ES, Wang TY, Rao SV, et al. Frequency and predictors of drug-eluting stent use in saphenous vein bypass graft percutaneous coronary interventions: a report from the American College of Cardiology National Cardiovascular Data CathPCI registry. *JACC Cardiovasc Interv*. 2010;3:1068-1073.
80. Harskamp RE, Beijl MA, Damman P, Tijssen JG, Lopes RD, de Winter RJ. Prehospitalization antiplatelet therapy and outcomes after saphenous vein graft intervention. *Am J Cardiol*. 2013;111:153-158.
81. Sachdeva A, Bavisetty S, Beckham G, et al. Discontinuation of long-term clopidogrel therapy is associated with death and myocardial infarction after saphenous vein graft percutaneous coronary intervention. *J Am Coll Cardiol*. 2012;60:2357-2363.
82. Redfors B, Genereux P, Witzensichler B, et al. Percutaneous coronary intervention of saphenous vein graft. *Circ Cardiovasc Interv*. 2017;10:e004953.

83. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315:1735-1749.
84. Sachdeva R, Aleti S, Thai H. Radial stent deformation in saphenous vein graft. *EuroIntervention*. 2012;8:876-877.
85. Nikolakopoulos I, Vemou E, Xenogiannis I, Brilakis ES. Successful rotational atherectomy of an undilatable ostial saphenous vein graft lesion. *J Invasive Cardiol*. 2020;32:E219.
86. Oknes A, McEntegart M. Intravascular lithotripsy in saphenous vein grafts and graft stent failure: a case series. *Catheter Cardiovasc Interv*. 2021;97(7):E945-E950.
87. Wolny R, Mintz GS, Matsumura M, et al. Intravascular ultrasound assessment of in-stent restenosis in saphenous vein grafts. *Am J Cardiol*. 2019;123:1052-1059.
88. Varghese I, Boatman DM, Peters CT, et al. Impact on contrast, fluoroscopy, and catheter utilization from knowing the coronary artery bypass graft anatomy before diagnostic coronary angiography. *Am J Cardiol*. 2008;101:1729-1732.
89. Eisenhauer MD, Malik JA, Coyle LC, Arendt MA. Impact of aorto-coronary graft markers on subsequent graft patency: a retrospective review. *Catheter Cardiovasc Diagn*. 1997;42:259-261.
90. Michael TT, Alomar M, Papayannis A, et al. A randomized comparison of the transradial and transfemoral approaches for coronary artery bypass graft angiography and intervention: the RADIAL-CABG Trial (RADIAL Versus Femoral Access for Coronary Artery Bypass Graft Angiography and Intervention). *JACC Cardiovasc Interv*. 2013;6:1138-1144.
91. Tsigkas G, Makris A, Tsiafoutis I, et al. The L-RECORD Study. *JACC Cardiovasc Interv*. 2020;13:1014-1016.
92. Brilakis ES. *Manual of Percutaneous Coronary Intervention: A Step-by-Step Approach*. Elsevier; 2020.
93. Farooq V, Mamas MA, Fath-Ordoubadi F, Fraser DG. The use of a guide catheter extension system as an aid during transradial percutaneous coronary intervention of coronary artery bypass grafts. *Catheter Cardiovasc Interv*. 2011;78:847-863.
94. Michael TT, Brilakis ES. Taming saphenous vein grafts using guide catheter extensions. *Catheter Cardiovasc Interv*. 2011;78:864-865.
95. Cooper L, Banerjee S, Brilakis ES. Crossover from radial to femoral access during a challenging percutaneous coronary intervention can make the difference between success and failure. *Cardiovasc Revasc Med*. 2010;11:266.e5-8.
96. Abdel-Karim AR, Banerjee S, Brilakis ES. Percutaneous intervention of acutely occluded saphenous vein grafts: contemporary techniques and outcomes. *J Invasive Cardiol*. 2010;22:253-257.
97. Cook J, Uretsky BF, Sachdeva R. Intervention in the occluded vein graft: with high risk can come great reward. Review of techniques with case examples. *J Invasive Cardiol*. 2012;24:612-617.
98. Giugliano GR, Falcone MW, Mego D, et al. A prospective multicenter registry of laser therapy for degenerated saphenous vein graft stenosis: the COronary graft Results following Atherectomy with Laser (CORAL) trial. *Cardiovasc Revasc Med*. 2012;13:84-89.
99. Garcia-Tejada J, Jurado-Roman A, Hernandez F, et al. Guiding-catheter thrombectomy combined with distal protection during primary percutaneous coronary intervention of a saphenous vein graft. *Cardiovasc Revasc Med*. 2013;14:356-358.
100. Fiorina C, Meliga E, Chizzola G, et al. Early experience with a new approach for percutaneous intervention of totally occluded saphenous vein graft: is the flow the best thrombolytic? *EuroIntervention*. 2010;6:461-466.
101. Al-Lamee R, Ielasi A, Latib A, et al. Clinical and angiographic outcomes after percutaneous recanalization of chronic total saphenous vein graft occlusion using modern techniques. *Am J Cardiol*. 2010;106:1721-1727.
102. Jim MH, Ho HH, Ko RL, et al. Paclitaxel-eluting stents for chronically occluded saphenous vein grafts (EOS) study. *J Interv Cardiol*. 2010;23:40-45.
103. Mhatre A, Uretsky BF, Sachdeva R. Substrate for complications. *J Invasive Cardiol*. 2012;24:E153-E156.
104. Garg N, Hakeem A, Gobal F, Uretsky BF. Outcomes of percutaneous coronary intervention of chronic total saphenous vein graft occlusions in the contemporary era. *Catheter Cardiovasc Interv*. 2014;83:1025-1032.
105. Ellis SG, Brenner SJ, DeLuca S, et al. Late myocardial ischemic events after saphenous vein graft intervention—importance of initially “nonsignificant” vein graft lesions. *Am J Cardiol*. 1997;79:1460-1464.
106. Rodes-Cabau J, Bertrand OF, Larose E, et al. Comparison of plaque sealing with paclitaxel-eluting stents versus medical therapy for the treatment of moderate nonsignificant saphenous vein graft lesions. The Moderate VEIn Graft LEsion Stenting with the Taxus Stent and Intravascular Ultrasound (VELETI) pilot trial. *Circulation*. 2009;120:1978-1986.
107. Abdel-Karim AR, Da Silva M, Lichtenwalter C, et al. Prevalence and outcomes of intermediate saphenous vein graft lesions: findings from the stenting of saphenous vein grafts randomized-controlled trial. *Int J Cardiol*. 2013;168:2468-2473.
108. Weerts J, Pustjens T, Amin E, et al. Long-term outcome after deferred revascularization due to negative fractional flow reserve in intermediate coronary lesions. *Catheter Cardiovasc Interv*. 2021;97:247-256.
109. Almomani A, Pothineni NV, Edupuganti M, et al. Outcomes of fractional flow reserve-based deferral in saphenous vein graft narrowing. *Am J Cardiol*. 2018;122:723-728.
110. Rodes-Cabau J, Bertrand OF, Larose E, et al. Five-year follow-up of the plaque sealing with paclitaxel-eluting stents vs medical therapy for the treatment of intermediate nonobstructive saphenous vein graft lesions (VELETI) trial. *Can J Cardiol*. 2014;30:138-145.
111. Nairouz R, Parzynski CS, Curtis JP, et al. Contemporary trends, predictors and outcomes of perforation during percutaneous coronary intervention (from the NCDR Cath PCI Registry). *Am J Cardiol*. 2020;130:37-45.
112. Sapontis J, Salisbury AC, Yeh RW, et al. Early Procedural and health status outcomes after chronic total occlusion angioplasty: a report from the OPEN-CTO Registry (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures). *JACC Cardiovasc Interv*. 2017;10:1523-1534.
113. Karatasakis A, Akhtar YN, Brilakis ES. Distal coronary perforation in patients with prior coronary artery bypass graft surgery: the importance of early treatment. *Cardiovasc Revasc Med*. 2016;17:412-417.
114. Wilson WM, Spratt JC, Lombardi WL. Cardiovascular collapse post chronic total occlusion percutaneous coronary intervention due to a compressive left atrial hematoma managed with percutaneous drainage. *Catheter Cardiovasc Interv*. 2015;86:407-411.
115. Chen DY, Chen CC, Hsieh IC. Hemoptysis caused by saphenous vein graft perforation during percutaneous coronary intervention. *J Invasive Cardiol*. 2013;25:E8-E10.
116. Marmagkiolis K, Brilakis ES, Hakeem A, Cilingiroglu M, Bilodeau L. Saphenous vein graft perforation during percutaneous coronary intervention: a case series. *J Invasive Cardiol*. 2013;25:157-161.
117. Yeo KK, Azarbal F, Zakrofsky P, et al. Differential longitudinal outcomes following percutaneous coronary intervention to the left internal mammary artery and other bypass grafts of the LAD: findings from the NCDR. *J Invasive Cardiol*. 2020;32:E143-E150.
118. Lichtenwalter C, Banerjee S, Brilakis ES. Dual guide catheter technique for treating native coronary artery lesions through tortuous internal mammary grafts: separating equipment delivery from target lesion visualization. *J Invasive Cardiol*. 2010;22:E78-E81.
119. Dimas B, Lindsey JB, Banerjee S, Brilakis ES. ST-Segment elevation acute myocardial infarction due to severe hypotension and proximal left subclavian artery stenosis in a prior coronary artery bypass graft patient. *Cardiovasc Revasc Med*. 2009;10:191-194.
120. Brilakis ES, Banerjee S. Novel uses of the Proxis embolic protection catheter. *Catheter Cardiovasc Interv*. 2009;74:438-445.



12 Calcified Lesions

AMAR KRISHNASWAMY AND CLAIRE E. RAPHAEL

INTRODUCTION, 222

ROTATIONAL ATHERECTOMY, 222

Procedural Details, 222

Clinical Studies of Rotational
Atherectomy, 224

Summary, 224

ORBITAL ATHERECTOMY, 226

Procedural Details, 226

Clinical Studies of Orbital Atherectomy, 226
Summary, 226

SCORING BALLOON ANGIOPLASTY, 227

Clinical Studies of Scoring Balloon
Angioplasty, 227

Summary, 227

EXCIMER LASER ATHERECTOMY, 227

Procedural Details, 229

Clinical Studies of Excimer Laser
Atherectomy, 229

Summary, 231

INTRACORONARY LITHOTRIPSY, 231

Clinical Studies of Intravascular
lithotripsy, 232

CONCLUSIONS, 232

INTRODUCTION

Calcified coronary lesions present an important challenge to interventional cardiologists. Because of the rigidity and noncompliance of a heavily calcified coronary artery segment, heavy calcification is a risk factor for stent thrombosis and ischemic target lesion revascularization (TLR) after percutaneous coronary intervention (PCI).¹⁻³

In the setting of severe luminal narrowing or speculated calcification obstructing the vessel lumen, the operator may be unable to pass balloons or stents. Fibrocalcific plaque is often difficult to dilate, reducing acute luminal gain and therefore limiting stent expansion. This in turn increases the risks of restenosis as well as stent thrombosis.^{4,5} Specialized techniques have been developed to modify severely calcified segments and include percutaneous transluminal rotational atherectomy (RA), orbital atherectomy (OA), scoring balloon and cutting balloon angioplasty (SBA and CBA), intravascular lithotripsy (IVL), and excimer laser coronary atherectomy (ELCA).

ROTATIONAL ATHERECTOMY

High-speed RA was introduced in the 1980s by David Auth as a mechanism to ablate atheromatous plaque by advancing a rapidly spinning, diamond-coated burr. RA was approved for coronary use by the Food and Drug Administration (FDA) in 1993. The procedure uses the principle of “differential cutting” in which the atherectomy device preferentially ablates inelastic tissue composed of fibrotic or calcific components and is safely deflected by more elastic tissue. The technique was intended to improve acute luminal gain with less deep wall injury compared with balloon angioplasty alone, which in turn should logically reduce the risk of restenosis. In the contemporary stent era, RA was further expected to reduce in-stent restenosis because of a reduction in residual plaque burden and improved apposition between the stent and vessel wall.

Procedural Details

Two Rotablator systems are currently available, the ROTABLATOR and ROTAPRO (Boston Scientific). Both consist of a 4.3-Fr, 135-cm drive shaft with a brass burr coated with small diamond crystals on the leading surface (Figure 12.1). The difference lies in the location of the on/off and DynaGlide buttons. Whereas the ROTAPRO uses a button on the advancer knob to activate and deactivate rotation of the burr, DynaGlide is selected using a button at the back of the body of the advancer system. The ROTABLATOR uses a foot pedal for activation and deactivation and to switch between dynaglide and full-speed rotation.

For both systems, the drive shaft is loaded onto a rota wire, which passes through the body of the rota system, and the burr is advanced slowly forward into the vessel, switched onto full-speed rotation, and then moved gently back and forth at the lesion using the advancer knob to “peck” at the lesion. Run times are limited to 15 to 30 seconds. During advancement, forward pressure applied to the burr is monitored carefully to minimize RPM drops greater than 5000 from baseline. Large RPM drops are associated with heat production and an increase in particulate size. After each run, the burr is disengaged from the lesion, and forward flow is restored for at least 20 to 30 seconds to allow ST segments to normalize and systemic vasodilation to resolve. Runs are repeated until the lesion is fully crossed and ablated.

The rota systems are connected to a tank of compressed nitrogen that is delivered to the console at 90 to 110 PSI to spin the Rotablator turbine and burr. The gas tank should contain at least 500 PSI of pressure. Delivery of the compressed gas to the burr is regulated by pressing DynaGlide the advancer knob for the ROTAPRO and by depression of the operator’s foot pedal for the ROTABLATOR.

The coronary artery is first wired, either directly using either the RotaWire Floppy or RotaWire Extra Support guidewire or using a workhorse wire and a microcatheter and then switching out to a RotaWire. Choice of Floppy vs Extra Support Rota wire depends on the characteristics of the vessel and lesion. Both consist of a 0.009-inch body



FIGURE 12.1 Rotablator rotational atherectomy system. **A**, Diamond-coated burr. **B**, Rotablator console. **C**, Rotalink advancer system with advancing knob (arrow). **D**, ROTAPRO system (on/off button on console). **E**, ROTAPRO console. Image provided courtesy of Boston Scientific. © 2023 Boston Scientific Corporation or its affiliates. All rights reserved.

and a 0.014-inch tip. The floppy wire is used most commonly and straightens the vessel less than the extra support RotaWire, an important consideration in tortuous vessels in which a stiffer wire may induce “pseudo” stenoses and increase the risk of vessel trauma by the burr.

The Rota system is loaded onto the rota wire, and the burr is advanced along the wire and then tested before insertion into the back of the guide. The operator should confirm that the rotaflush is seen dripping through the drive shaft. The burr should be tested and intended RPM set on the console, usually 150,000 to 180,000 RPM. To do this, the brake is placed on the wire, the burr is held above the patient’s drape, the turbine is activated, and the nurse or technician turns the power dial until the desired baseline RPM is achieved. The Rotablator system is then advanced over the wire to a position just proximal of the lesion of interest. This is usually done as a two-person process, with one operator holding the wire and disengaging the “brake” as the other advances the system through the guide, as with an over-the-wire balloon or microcatheter.

When the burr is in place in the proximal aspect of the artery, the operator activates the turbine and advances the burr slowly and steadily back and forth across the lesion. It is important that the burr is withdrawn completely from the lesion before deactivating the turbine because mistiming this sequence can cause the burr to become entrapped in the calcified lesion. Pushing the burr too firmly or allowing stored tension on the wire to lurch the burr suddenly forward can cause the rotating burr to pass through the lesion without adequate ablation. This may cause the burr to become entrapped distal to the intended lesion.

After the atherectomy is completed, the system is removed with the DynaGlide mode activated, which provides a 60,000- to 90,000-RPM spin of the burr to facilitate extraction of the system over the wire. The brake is disengaged, and the system is removed. This step is most safely performed under continuous fluoroscopy to assure wire position in the vessel.

The choice of initial burr size is dependent on the lesion and the size of the coronary vessel. To minimize complications such as coronary dissection and perforation, it is recommended that the operator not exceed a burr-to-artery diameter ratio greater than 0.7. Operators may start with a 1.25-, 1.5-, or 1.75-mm burr to create a channel across the lesion. The necessary guide catheter size for each burr is given in [Table 12.1](#). An example video case is detailed in [Videos 12.1 to 12.4](#).

Complications from RA include microvascular occlusion by distal embolization of debris from the lesion and poor or no reflow. To reduce this risk, a continuous pressurized intracoronary infusion of a rotaflush solution is circulated through the rota catheter. This usually consists

TABLE 12.1 Guide Catheter Requirement for Intended Rotational Atherectomy Burr Size

ROTABLATOR BURR SIZE (mm)	MINIMAL LUMEN GUIDE SIZE (Fr)
1.25–1.75	6
2.00	7
2.15–2.25	8
2.38–2.5	9

of the proprietary Rotaglide lubricant to reduce heat generation, a calcium channel blocker (verapamil or nifedipine), and nitroglycerin. Rotaglide should not be used in patients who are allergic to eggs or olive oil because both are constituents of the lubricant. Hemodynamic instability may preclude the use of verapamil or nitroglycerin in the solution.

Hemolysis from RA may also promote generation of adenosine and other substances that affect electrical conduction and may induce heart block. Intravenous infusion of aminophylline with or without an atropine bolus during runs may also be helpful. A temporary pacemaker may be placed before extensive RA of the right coronary artery or a dominant left circumflex coronary artery (LCX).

Clinical Studies of Rotational Atherectomy

The first trials of RA compared it with balloon angioplasty in all patients who needed PCI. There was no benefit in terms of luminal area or plaque modification. Landmark trials were largely in the pre-stent era and are summarized in Table 12.2. The PREPARE-CALC (comparison of strategies to prepare severely calcified coronary lesions) study showed higher procedural success using RA compared with cutting or scoring balloons but with similar rates of TVR on follow-up.⁶

Summary

The PREPARE-CALC study demonstrated that RA was associated with higher rates of procedural success compared with scoring or cutting balloons; however, there are no

TABLE 12.2 Trials of Rotational Atherectomy

STUDY	STUDY DESIGN	PATIENTS (n)	PRIMARY ENDPOINT	RESULTS
ERBAC (Reifart et al. ⁸)	- Design: single-study, open-label trial of laser atherectomy vs RA vs balloon angioplasty - Inclusion: patients with symptomatic coronary disease warranting elective PCI for a complex lesion	685	Procedural success defined as diameter stenosis <50% and absence of death, Q-wave MI, or CABG	- Procedural success: RA had higher rates than laser atherectomy or balloon angioplasty (89% vs 77% and 80%; $P = .0019$) - No difference in major (in-hospital) complications between groups - At 6-mo follow-up, TLR was more common in the RA (42%) and laser atherectomy (46%) compared with balloon angioplasty (32%; $P = .13$)
COBRA (Dietz et al. ⁹)	- Design: multicentre RCT of balloon angioplasty (PTCA) vs RA - Inclusion: patients with angiographically predefined complex coronary artery lesions	502	Procedural success, 6-mo restenosis rates in the treated segments and MACE during follow-up	- Procedural success rates were 78% for PTCA and 85% for RA ($P = .038$) - Crossover from PTCA to RA was 4% - Crossover from RA to PTCA was 10% - No difference in MACE, but more stents were required after PTCA compared with RA - At 6 mo, TVR and restenosis rates were similar (51% vs 49%; $P = .33$)
CARAT (Safian et al. ¹⁰)	RCT of small vs large-bore RA	222	Final diameter stenosis at end of procedure	- No difference in procedural success between groups - Similar immediate lumen enlargement - Similar in-hospital ischemic complications or late TVR - Patients randomized to large burrs had more significant angiographic complications (13% vs 5%; $P < .05$)
STRATAS (Whitlow et al. ¹¹)	- Design: RCT of an "aggressive" strategy (maximum burr-to-artery ratio >0.70 alone, with adjunctive balloon inflation ≤ 1 atm), or a "routine" strategy (maximum burr-to-artery ratio ≤ 0.70 and routine balloon inflation ≥ 4 atm) - Patients with stable coronary artery disease being considered for PCI with coronary atherectomy	497	Minimum luminal diameter difference between treatment strategies at 6-mo follow-up	- Primary endpoint: no significant difference between groups - Final minimum lumen diameter and residual stenosis were 1.97 mm and 26%, respectively, for the routine strategy versus 1.95 mm and 27%, respectively, for the aggressive strategy - Clinical success was similar between groups. CK-MB was >5 times normal in 7% of the routine vs 11% of the aggressive group - CK-MB elevation was associated with a decrease in rpm of >5000 from baseline for >5 s - At 6 mo, 22% of the routine vs 31% of the aggressive strategy patients had TLR
ROTAXUS (Abdel-Wahab et al. ¹²)	Patients with complex calcified native coronary lesions were randomized to RA followed by stenting ($n = 120$) or stenting without RA ($n = 120$, standard therapy group) using a polymer-based slow-release paclitaxel-eluting stent	240	- Primary endpoint: in-stent late lumen loss at 9 mo - Secondary endpoints included angiographic and strategy success, binary restenosis, definite stent thrombosis, and MACE at 9 mo	- Primary endpoint: higher in-stent late lumen loss for RA (0.44 ± 0.58 vs 0.31 ± 0.52; $P = .04$) despite an initially higher acute lumen gain (1.56 ± 0.43 vs 1.44 ± 0.49 mm; $P = .01$) - Higher crossover in the standard therapy group compared with the RA group (12.5% vs 4.2%; $P = .02$), resulting in higher strategy success in the RA group (92.5% vs 83.3%; $P = .03$) - In-stent binary restenosis, TLR, definite stent thrombosis, and MACEs were similar between groups

TABLE 12.2 Trials of Rotational Atherectomy—cont'd

STUDY	STUDY DESIGN	PATIENTS (n)	PRIMARY ENDPOINT	RESULTS
PREPARE-CALC (Abdel-Wahab et al ⁶)	- Design: RCT of modifying balloons, MB (scoring or cutting balloons: Flextome, AngioSculpt, or Scoreflex) or RA - Inclusion: patients with documented myocardial ischemia and severely calcified native coronary lesions undergoing PCI	200	- Two primary endpoints: - Strategy success defined as successful stent delivery and expansion with attainment of <20% in-stent residual stenosis in the presence of TIMI 3 flow without crossover or stent failure; powered for superiority - In-stent late lumen loss at 9 mo, powered for noninferiority	- Higher success in the RA group (98% vs 81%; $P = .0001$), but mean fluoroscopy time was longer (19.6 ± 13.4 vs 23.9 ± 12.2 minutes; $P = .03$). - At 9 mo, mean in-stent late lumen loss were 0.16 ± 0.39 mm in the MB group and 0.22 ± 0.40 mm in the RA group ($P = .21$; $P = .02$ for noninferiority) - TLR (2% vs 7%; $P = .17$), definite or probable stent thrombosis (0% vs 0%; $P = 1.00$), and TVR (6% vs 8%; $P = .78$) were low and similar between the groups

CABG, Coronary artery bypass grafting; CARAT, Coronary Angioplasty and Rotablator Atherectomy Trial; CK-MB, creatine kinase-MB; COBRA, comparison of balloon-angioplasty versus rotational atherectomy study; ERBAC, Excimer Laser, Rotational Atherectomy, and Balloon Angioplasty Comparison; MACE, major adverse cardiac event; MB, modifier balloon; MI, myocardial infarction; PCI, percutaneous coronary intervention; PREPARE-CALC, comparison of strategies to prepare severely calcified coronary lesions; PTCA, percutaneous transluminal coronary angioplasty; RA, rotational atherectomy; RCT, randomized controlled trial; ROTAXUS, Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease; STRATAS, study to determine rotablator and transluminal angioplasty strategy; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization.

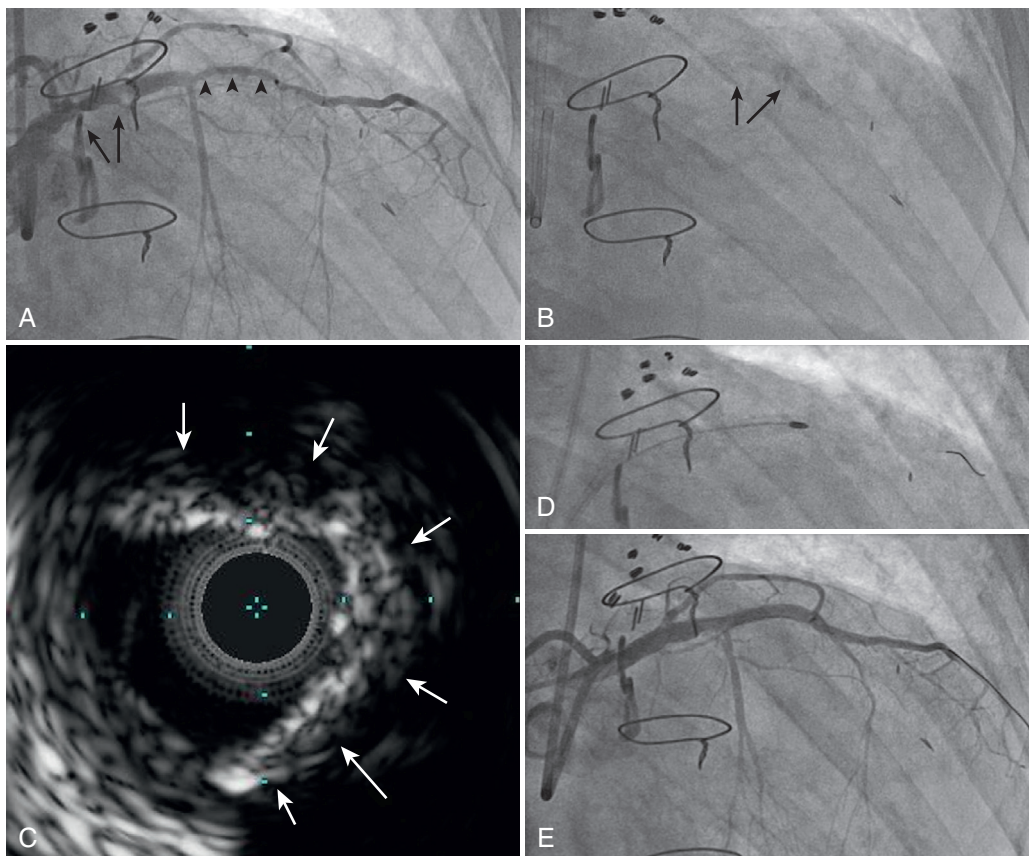


FIGURE 12.2 Rotational atherectomy of the left anterior descending coronary artery (LAD) diagonal. **A**, Initial angiogram demonstrates severe calcified stenosis in the proximal (arrow) and mid LAD (arrowheads) extending to the diagonal. **B**, Fluoroscopy alone shows the severe calcifications (arrows). **C**, Intravascular ultrasound demonstrates 270-degree calcification (arrows) with echo dropout behind the calcium. **D**, Rotaburr in the mid LAD. **E**, Final angiogram after stent placement.

data to suggest superior outcomes on long-term follow-up. RA should be reserved for cases in which optimal balloon and stent expansion is not possible without plaque modification (Figure 12.2). It may also be necessary for spiculated or severely narrowed lesions that do not allow the passage of balloons or stents or lesions that are not dilatable with noncompliant, high-pressure balloons. The 2011 American

College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) PCI guidelines provide a Class IIb recommendation for RA in “fibrotic or calcified lesions that might not be crossed by a balloon catheter or adequately dilated before stent implantation” and a Class III recommendation for RA “for de novo lesions or in-stent restenosis.”¹²

ORBITAL ATHERECTOMY

The Diamondback 360-degree coronary OA system (OAS, Cardiovascular Systems) is based on the principles of differential sanding and centrifugal force. The system consists of an eccentrically mounted, diamond-coated “crown” that orbits over a guidewire. A thin layer of plaque is “sanded” off with each pass of the device, and elastic tissue flexes away from the crown. The elliptical orbit of the devices is intended to allow microdebris to disperse, as opposed to the rota burr, which does not allow blood to flow past. The Micro Crown OAS is a second-generation device that incorporates a diamond-coated distal tip brushing to aid in engaging tight lesions (Figure 12.3). The diamond-coated distal tip is not offset and therefore does not generate an orbit. However, the more proximal tip produces an orbit similar to the classic Diamondback OA but at lower speeds, reducing the risk of thermal injury. The COAST (Coronary Orbital Atherectomy System Study) trial showed no difference in procedural success between the two devices.

Procedural Details

The OAS passes over the ViperWire guidewire. There are two wire options, the Viper wire Advance and the Viper

wire Advance with Flex Tip. The ViperWire Advance with Flex Tip has a flexible nitinol core with a shapeable floppy tip, which helps with primary wiring of the lesion. The OAS crown is available in 1.25- and 1.5-mm sizes, with a maximum orbit that is influenced by the rotational speed of the crown (1.82 and 2.16 mm for each, respectively). Similar to RA, a proprietary ViperSlide lubricant is continuously infused in addition to saline to provide lubrication, cooling, and flow of microdebris. An example video case in which RA was unsuccessful and needed to convert to OA is detailed in Videos 12.5 to 12.11.

Clinical Studies of Orbital Atherectomy

These studies are summarized in Table 12.3.

Summary

Orbital atherectomy in the coronary tree is a recently available and approved modality for the treatment of calcified lesions. Initial trial data are limited but appear promising with respect to safety and efficacy. The optimal use of the OAS remains to be defined by accumulating clinical experience and comparative clinical trials.



FIGURE 12.3 Orbital atherectomy system (A) Body of the device. The green button is pressed to activate device rotation. The classic crown (B). ©2023 Cardiovascular Systems, Inc. Images are used with permission from Cardiovascular Systems, Inc. Diamondback 360® Coronary Orbital Atherectomy System is a registered trademark of Cardiovascular Systems, Inc..

TABLE 12.3 Clinical Studies of Orbital Atherectomy

STUDY	STUDY DESIGN	PATIENTS (n)	PRIMARY ENDPOINT	RESULTS
Orbit I (Parikh et al. ¹³)	• Two-center nonrandomized study of OA in patients with de novo calcified coronary lesions	50	—	• 94% procedural success; in-hospital MACE, 4% (two non-Q-wave MIs); 30 day MACE, 6% (one additional non-Q-wave MI); 8% at 6 mo (one additional cardiac death); six coronary dissections, one coronary perforation
Orbit II (Chambers et al. ¹⁴)	• Prospective multicenter nonblinded single-arm study of OA in patients with severely calcified lesions	443	• Residual stenosis <50% after stent without in hospital major adverse events	• Met primary safety and efficacy endpoints; 98% procedural success; in-hospital MACE: Q-wave MI (0.7%), cardiac death (0.2%), TVR (0.7%)
COAST (Redfors et al. ¹⁵)	• Prospective multicenter nonblinded single-arm study of the Micro Crown OA system in patients with severely calcified lesions	100	• Procedural success defined as stent delivery with <50% residual stenosis without in-hospital MACE • Safety endpoint: freedom from MACE at 30 days	• 85% procedural success; freedom from MACE at 30 days in 85% of cases; freedom from MACE was 78% at 1 y

COAST, Coronary Orbital Atherectomy System Study; MACE, major cardiovascular adverse event; MI, myocardial infarction; OA, orbital atherectomy; TVR, target vessel revascularization.

SCORING BALLOON ANGIOPLASTY

Scoring balloon angioplasty is a generic term that refers to inflating a balloon catheter with one or more protruding metallic edges contacting the vessel wall on balloon dilation. The leading metallic edge is designed to cut or score the plaque, causing a cleavage plane that theoretically enhances more controlled lumen dilation than routine balloon angioplasty. There are currently four major scoring balloons, detailed in [Figure 12.4](#).

The Flexotome and its later iteration, the Wolverine (Boston Scientific), are noncompliant balloons with three to four longitudinally positioned microsurgical metallic edges. These are designed to parallel the balloon when the balloon is deflated and then angle outward toward the vessel wall as the balloon expands to create controlled micro-incisions in the calcified plaque. The Wolverine has a lower profile and is designed to improve deliverability and can be delivered via 5-Fr catheter. The height of the blades from the surface of the balloon is also lower in profile compared with the Flexotome, allowing for more controlled plaque modification.

The AngioSculpt balloon catheter (Angioscore) consists of a semicompliant nylon balloon surrounded by an expandable nitinol cage. Upon inflation, the nitinol scoring elements are driven into the arterial wall and concentrate the dilating force to the protruding metallic edges. Theoretically, the concentration of outward force into the small surface area of the nitinol frame focuses the dilating force and enhances vessel lumen expansion. In addition, the metal surfaces are driven into the arterial wall, expediting lumen expansion.

The Chocolate XD Balloon (Medtronic) is a semicompliant balloon with a constraining nitinol cage over the surface of the balloon. This creates a “groove and pillow” topography that is intended to be less traumatic than other scoring balloons as well as minimizing the risk of “dog boning” of the balloon.

Scoring balloons are sized 1:1 to the vessel and inflated to low pressures (typically 6 atm). Instructions for use suggest a slow inflation, leaving the balloon inflated for approximately 60 seconds followed by slow deflation. Scoring balloon inflation sometimes leads to less elastic recoil and more luminal enlargement than dilation with a similar size, noncompliant, high-pressure balloon in ostial or resistant coronary lesions.¹⁶

Clinical Studies of Scoring Balloon Angioplasty

The largest randomized trial of stand-alone CBA versus percutaneous transluminal coronary angioplasty (PTCA)

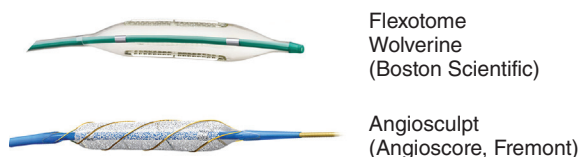


FIGURE 12.4 Types of scoring balloons. Image provided courtesy of Boston Scientific. © 2023 Boston Scientific Corporation or its affiliates. All rights reserved.

showed no clinical advantage of CBA in angiographic restenosis or TVR but a significant increase in acute vessel perforation and tamponade.¹⁷ CBA today is generally used to predilate resistant coronary lesions before stent placement or to dilate in-stent restenosis lesions to prevent balloon slippage. CBA can effectively dilate mild to moderately calcified resistant coronary lesions but not dense superficial calcification.

De Ribamar Costa and colleagues¹⁸ compared the adequacy of drug-eluting stent (DES) expansion by intravascular ultrasonography (IVUS) with direct stenting, predilation with a noncompliant balloon, or predilation with the AngioSculpt in 299 consecutive de novo lesions. The minimum stent diameter (2.6 ± 0.4 , 2.5 ± 0.4 , 2.8 ± 0.4 mm) and minimal stent cross-sectional area (6.0 ± 1.7 , 5.9 ± 1.6 , 6.8 ± 1.6 mm²) were significantly better in the AngioSculpt pretreatment group. In addition, a minimum DES area smaller than 5.0 mm² (associated with increased restenosis and acute stent thrombosis) was found in only 11% of AngioSculpt-pretreated lesions versus 26% of the remaining lesions. The authors concluded that AngioSculpt pretreatment before DES placement enhances stent expansion ([Table 12.4](#)).¹⁹

Summary

Lesion modification with SBA often results in successful dilation of a resistant coronary lesion and enhances stent expansion. Because of the ease of use and effectiveness of SBA, these devices have become frequently used for lesion modification in catheterization laboratories.

Because of simplicity of use and cost, SBA is frequently used to dilate ostial lesions (which are traditionally considered as noncompliant or may have an unfavorable guide-to-wire angle for atherectomy) or mild to moderately calcified vessels that would be expected to be difficult to dilate. In these situations, inadequate expansion of the scoring balloon should prompt consideration of another plaque modification strategy. A case example of a very heavily calcified ostial right coronary artery lesion treated with SBA is shown in [Figure 12.5](#). Additionally, SBA may be beneficial to minimize “slipping” of traditional balloons during dilation of in-stent restenotic lesions.

EXCIMER LASER ATHERECTOMY

Laser technology was approved for use in the coronary tree by the FDA in 1992. The contemporary excimer coronary laser operates in the ultraviolet field ($\lambda = 308$ nm), which minimizes vapor bubble formation and improves the safety profile of the device compared with older generation devices that operated in the infrared field ($\lambda = 2090$ nm).²¹ The application of laser energy to the vessel results in photochemical, photomechanical, and photothermal interactions that produce gas vapor and acoustic shockwaves within the tissue that ultimately provides a debulking effect. Applications of ELCA include uncrossable chronic total occlusions, balloon-resistant calcified lesions, and underexpanded stent lesions.

TABLE 12.4 Clinical Trials of Scoring Balloons

STUDY	STUDY DESIGN	PATIENTS (n)	PRIMARY ENDPOINT	RESULTS
Cutting Balloon Global Randomized Trial (Mauri et al. ¹⁷)	- Design: multicenter, randomized trial comparing the incidence of restenosis after CB angioplasty vs conventional balloon angioplasty - Inclusion: myocardial ischemia attributable to a de novo stenosis <20 mm in length in a native coronary artery ≥ 2 mm in diameter	617	- Primary endpoint: 6-mo binary angiographic restenosis rate - Acute procedural success: defined as <50% diameter stenosis without in-hospital MACEs	- Primary endpoint: 6-mo binary restenosis rates were 31.4% for CB and 30.4% for PTCA ($P = .75$) - Acute procedural success rates were 92.9% for CB and 94.7% for PTCA ($P = .24$) - Freedom from TVR was slightly higher in the CB arm (88.5% vs 84.6%, log-rank $P = .04$); five coronary perforations occurred in the CB arm only (0.8% vs 0%; $P = .03$) At 270 days, rates of MI, death, and total MACE for CB and PTCA were 4.7% vs 2.4% ($P = .03$), 1.3% vs 0.3% ($P = .06$), and 13.6% vs 15.1% ($P = .34$)
REDUCE III (Ozaki et al. ²⁰)	- Design: RCT of CBA before BMS (CBA-BMS) or BA before BMS (BA-BMS) - Inclusion: patients with unstable or stable angina, a single target lesion in a native coronary artery with a vessel diameter <4 mm, and planned stent implantation with up to two stents	521	- Primary endpoint: angiographic restenosis: defined as $\geq 50\%$ diameter stenosis at follow-up by quantitative coronary angiography - Secondary endpoint: subsequent TLR at follow-up	- Primary endpoint: minimal lumen diameter was significantly greater in CBA-BMS than BA-BMS (2.65 ± 0.40 mm vs 2.52 ± 0.4 mm; $P < .01$) and percent diameter after stenosis was less in CBA-BMS than BA-BMS ($14.0 \pm 5.9\%$ vs $16.3 \pm 6.8\%$, $P < .01$) - Restenosis (11.8% vs 19.6%; $P < .05$) and TLR (9.6% vs 15.3%; $P < .05$) were significantly lower in CBA-BMS than BA-BMS

BA, Balloon angioplasty; BMS, bare-metal stent; CBA, cutting balloon angioplasty; MACE, major adverse cardiac event; PTCA, percutaneous transluminal coronary angioplasty; RCT, randomized controlled trial; REDUCE III, A prospective randomized multicenter trial comparing CBA with balloon angioplasty (BA) before stenting; TLR, target lesion revascularization.

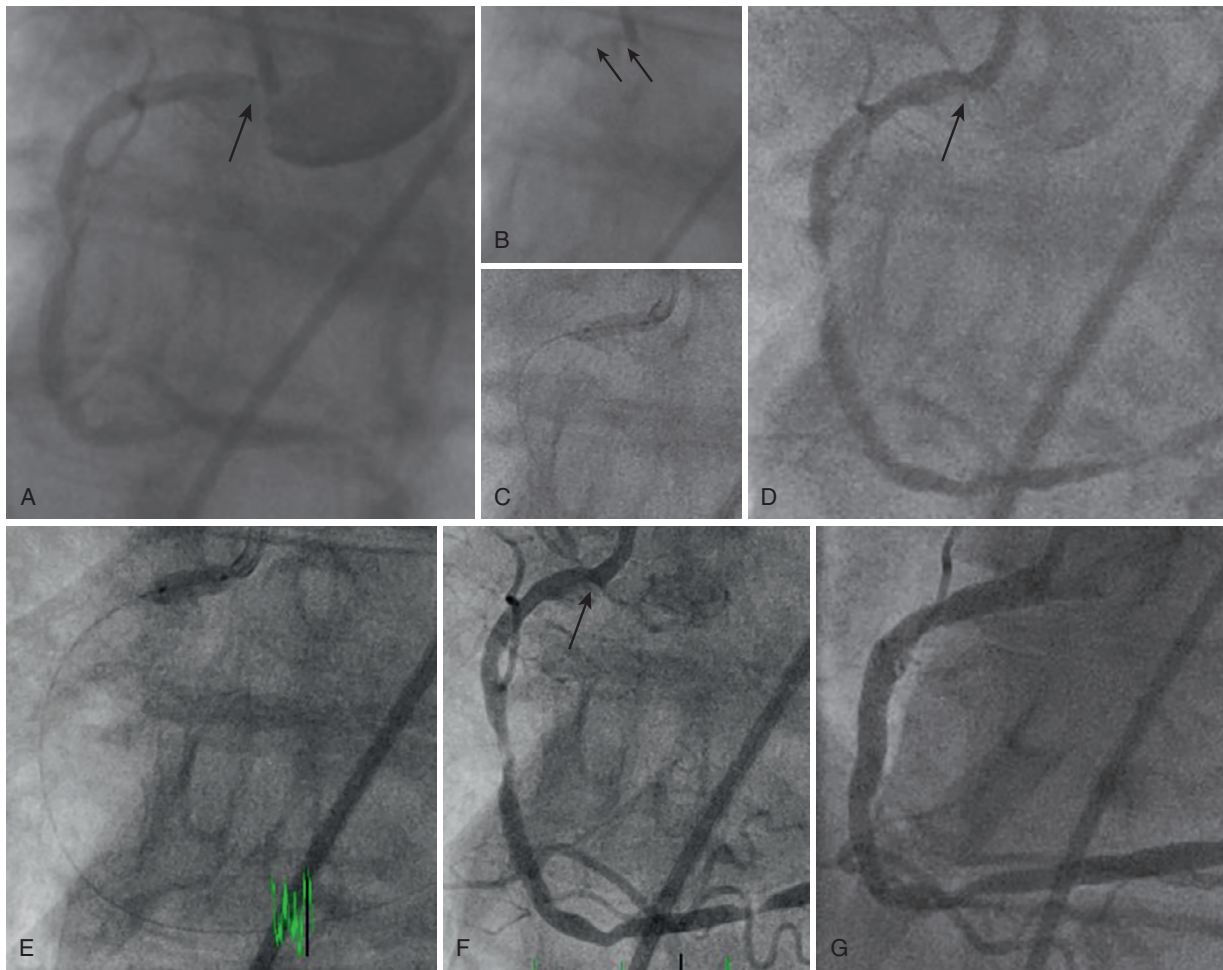


FIGURE 12.5 Scoring balloon angioplasty before stent placement. Angiography (A) demonstrates a severe ostial right coronary artery (arrow) stenosis with severe calcification fluoroscopically (B). Routine balloon angioplasty (C) provided only mild improvement (D) in lumen size with difficulty in passing a stent. AngioSculpt scoring angioplasty (E) resulted in calcium fracture and improved lumen gain (F), facilitating stent placement (G).

Procedural Details

The Spectranetics CVX-300 ELCA system (Spectranetics) consists of the generator console (Figure 12.6), the laser catheter, and the activating pedal. The catheter is available in 0.9-, 1.4-, 1.7-, and 2.0-mm diameters with specifications as provided in Table 12.5. Before insertion of the laser catheter into the guide, the operator must calibrate the system by aiming the catheter at the energy detector and stepping on the foot switch. When calibration is complete, the console will state that calibration is “OK” and the system is “Ready.”

As with any other catheter, the lesion of interest must first be crossed with a coronary guidewire. A laser catheter is then chosen, which is optimally two-thirds of the size of the target vessel. For native, unstented coronary arteries, the most common catheter used is the 0.9-mm one, often at a starting setting of 4 0mJ/mm² and 40 Hz, which can be increased to 80 mJ/mm² and 80 Hz if required. For in-stent restenosis, higher energies are often needed, and some operators prefer to start at 80 mJ/mm² and 80 Hz. If a 1.4-mm catheter is used, suggested initial settings are a fluence of 30 mJ/mm² at a rate of 20 Hz.

The laser is then slowly advanced across the lesion. Unlike RA, which debulks only while being advanced, the laser catheter provides energy during advancement and retraction of the catheter, both of which should be performed slowly to optimize energy delivery. Caution should be used to perform continuous saline injection in the guide catheter while lasering. This reduces the temperature and uncontrolled photomechanical damage in the coronary artery, thereby minimizing complications. The connection of a saline pressurized bag to the guiding catheter via a Tuohy Borst adapter is frequently used for this purpose.

Specific situations may call for contrast injection at the time of lasing, as discussed later.

Clinical Studies of Excimer Laser Atherectomy

As with RA, nonrandomized studies of ELCA provided seemingly hopeful results for atherectomy as an alternative to PTCA alone. However, randomized trials of ELCA versus PTA failed to demonstrate significant benefit (Table 12.6).

An important use of ELCA today is for patients with in-stent restenosis (ISR) associated with an underexpanded stent. In fibrotic or calcified lesions that have not been properly prepared with debulking, predilation, or plaque modification before stent placement, achieving appropriate stent expansion even with high-pressure deployment and noncompliant balloon dilation may not be possible. To facilitate adequate stent expansion, ELCA can be used to vaporize and modify the fibrotic or calcified plaque behind the stent, allowing subsequent expansion with noncompliant balloon dilation. Figure 12.7A demonstrates severe ISR in the proximal LCX and proximal ramus intermedius (RI) 8 months after 2.5-mm stent placement in each vessel. The LCX was adequately treated with noncompliant balloon dilation, but severe stenosis remained in the RI even after dilation with a 3.0-mm noncompliant balloon (Figure 12.7B). IVUS demonstrated severely calcified atheroma behind the stent and a minimum lumen area (MLA) within the stent of 2.7 mm² (Figure 12.7C). After ELCA, the same 3.0-mm noncompliant balloon yielded significantly greater dilation (Figure 12.7D), and IVUS demonstrated an MLA of 4.2 mm² (Figure 12.7E).

The use of ELCA to treat stent underexpansion was demonstrated in the Excimer Laser LEsion Modification to

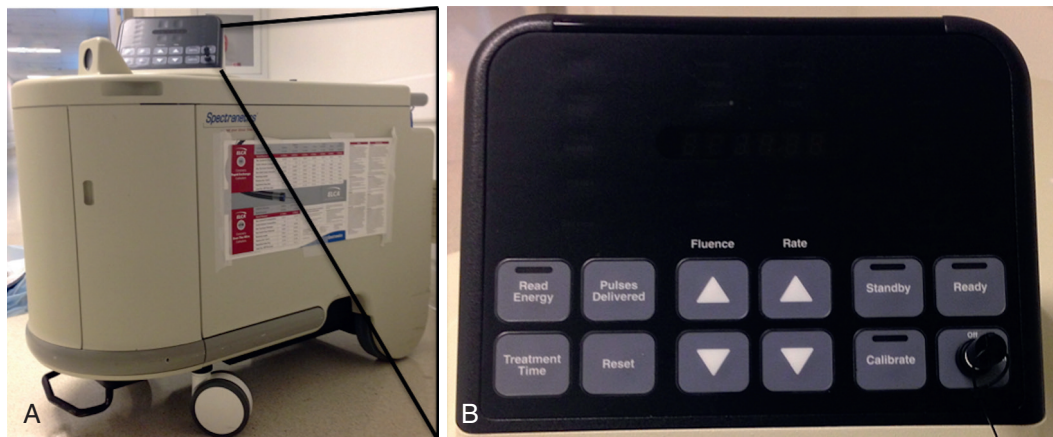


FIGURE 12.6 Spectranetics laser atherectomy console. (A) (arrow: energy detector) and main control display (B).

TABLE 12.5 Technical Specifications of the Spectranetics Excimer Laser Coronary Atherectomy Catheter System

LASER CATHETER	0.9 mm	1.4 mm	1.7 mm	2.0 mm
Guide catheter compatibility (Fr)	6	6	7	8
Minimum vessel diameter (mm)	2.0	2.2	2.5	3.0
Fluence (mJ/mm ²)	30–80	30–60	30–60	30–60
Repetition rate (Hz)	25–80	25–40	25–40	25–40

TABLE 12.6 Trials of Excimer Laser Coronary Atherectomy

STUDY	STUDY DESIGN	PATIENTS (n)	PRIMARY ENDPOINT	RESULTS
ERBAC (Reifart et al. ⁸⁾)	- Design: single-study open-label trial of laser atherectomy vs RA vs BA - Inclusion: patients with symptomatic coronary disease warranting elective PCI for a complex lesion	685	Procedural success defined as diameter stenosis <50% and absence of death, Q-wave MI, or CABG	- Primary endpoint: patients who underwent RA had higher rates of procedural success than those who underwent laser atherectomy or BA (89% vs 77% and 80%; $P = .0019$). - MACE: no difference in major in hospital complications between the groups At 6-mo follow-up, TLR was more common in the RA (42%) and laser atherectomy (46%) groups compared with the BA group (32%; $P = .13$)
AMRO (Appelman et al. ²²)	- Design: multicenter trial RCT of laser angioplasty followed by BA or BA alone - Inclusion: patients with stable angina and lesion >10 mm length	308	- Primary clinical endpoint: death, MI, CABG, or repeat angioplasty of the treated segment - Primary angiographic endpoint: minimal luminal gain at 6-mo follow-up	- Primary clinical endpoint: similar rates of MI, CABG, and repeat angioplasty between groups - Primary angiographic endpoint: net mean gain in mean lumen diameter was 0.4 ± 0.7 mm with laser angioplasty and BA and 0.48 ± 0.7 mm in BA alone - Similar rates of success (80% vs 79%) for laser angioplasty followed by BA compared with BA alone - Restenosis rates were numerically higher in the laser group compared with the BA-only group (52% vs 41%; $P = .13$)
LAVA (Stone et al. ²³)	- Design: multicenter trial RCT of laser angioplasty followed by BA vs BA alone - Inclusion: patients with stable or unstable angina	215	To define safety and efficacy of laser angioplasty	- High procedural success in both groups (96.6% vs 96.9%; $P = .88$) - No difference in postprocedural diameter stenosis after laser compared with BA alone (20% vs 15%; $P = .5$). - Laser resulted in significantly more MI and total in hospital major adverse events

AMRO, Amsterdam-Rotterdam Trial; BA, balloon angioplasty; CABG, coronary artery bypass grafting; ERBAC, Excimer Laser, Rotational Atherectomy, and Balloon Angioplasty Comparison; MI, myocardial infarction; PCI, percutaneous coronary intervention; RA, rotational atherectomy; RCT, randomized controlled trial; TLR, target vessel revascularization.

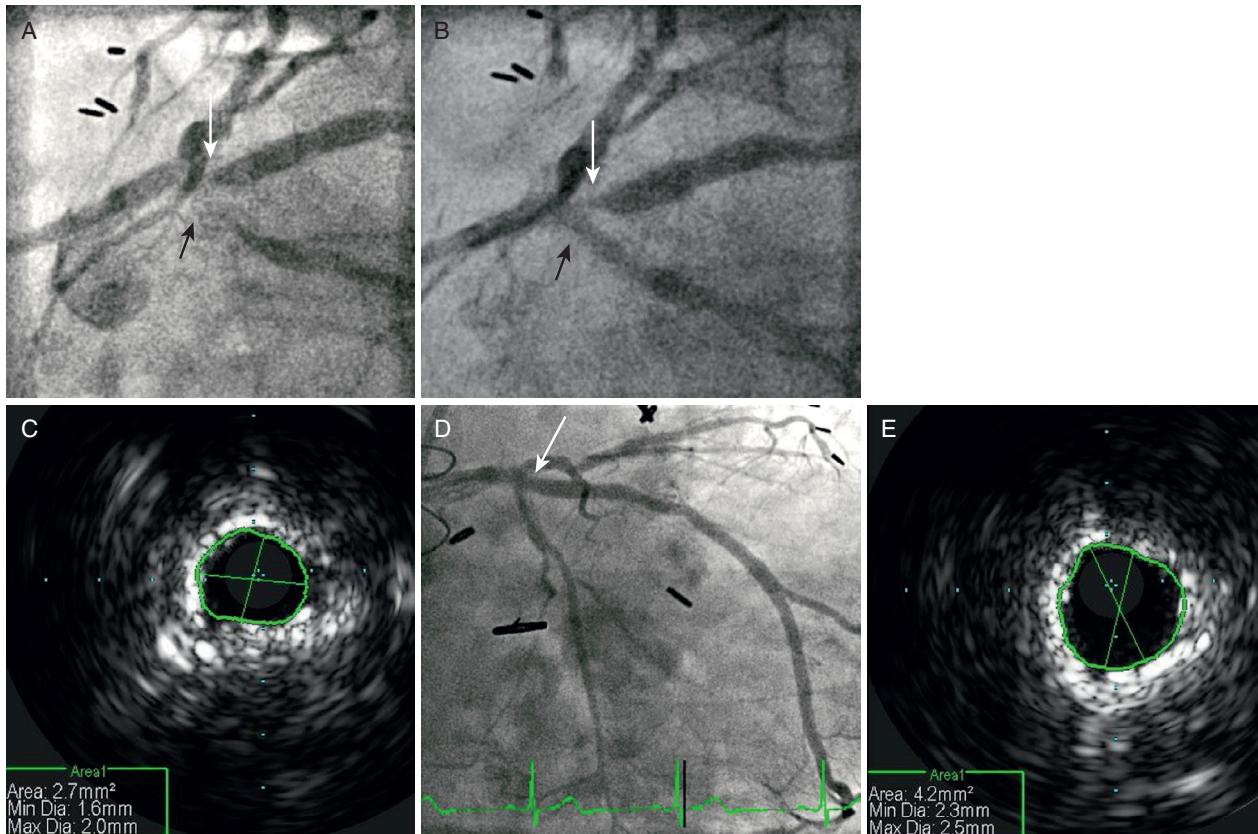


FIGURE 12.7 Excimer laser coronary atherectomy (ELCA) to treat in-stent restenosis (ISR) associated with stent underexpansion. **A**, Severe ISR in the proximal ramus (white arrow) and proximal left circumflex coronary artery (black arrow). **B**, Continued severe ISR in the ramus after percutaneous transluminal coronary angioplasty (PTCA) (3.0-mm balloon). **C**, Intravascular ultrasonography (IVUS) demonstrates severe calcification and fibrosis behind the stent (minimum lumen area [MLA], 2.7 mm²). **D**, Improved expansion after ELCA followed by PTCA (using the same 3.0-mm balloon) of the proximal RL. **E**, IVUS demonstrates improved stent expansion (MLA, 4.2 mm²).

Expand Non-dilatable sTents (ELLEMENT) registry by Latib and colleagues.²⁴ ELCA is routinely performed with simultaneous intracoronary saline infusion or injection to minimize heat generation and vapor bubble formation. However, these investigators instead demonstrated the use of simultaneous contrast injection to create a controlled “explosion” to improve stent expansion. In their series of 28 patients with undilatable stents treated with this method, 27 patients had successful dilation after ELCA (IVUS MSA increased from 3.5 to 7.1 mm²). The incidence of periprocedural MI was 3.6%, with a 6-month TLR rate of 3.6%, demonstrating the utility of this technique in appropriately selected patients without other options for further stent expansion.

Summary

Data do not support a greater benefit of laser atherectomy compared with PTA alone in “all comer” lesions. However, it does hold a role in the treatment of severely calcified lesions and stent underexpansion. These recommendations are reflected by the 2011 ACC/AHA/SCAI PCI guidelines, which provide a Class IIb recommendation for ELCA in “fibrotic or moderately calcified lesions that cannot be crossed or dilated with conventional balloon angioplasty” and a Class III recommendation for use “routinely during PCI.”¹²

INTRACORONARY LITHOTRIPSY

Intravascular lithotripsy (Shockwave Medical) is designed to selectively disrupt calcified tissue, fracturing it, while producing minimal damage to soft tissues. It was approved by the FDA for treatment of coronary artery calcification in 2021. Electrical emitters within the balloon cause vaporization of the 50:50 contrast solution and a rapidly expanding then contracting bubble, causing a sonic wave to be delivered to the local tissues. It is most effective where there is circumferential calcification. The sonic waves will

treat both deep and superficial coronary calcium. Advantages over atherectomy include a shorter learning curve, ability to deliver the system over a standard coronary wire, and less risk of distal embolization because the calcium fragments remain in situ rather than moving downstream.

The IVL balloon is delivered over a workhorse or any standard 0.014-inch coronary wire. It is licensed to use via a 6-Fr guide (although smaller balloons will fit through a 5-Fr guide) and will deliver through a 6-Fr guide extension, although this can be tight and larger balloons requiring a guide extension may be easier to deliver via a 7-Fr system. An example case is shown in [Figure 12.8](#).

The balloon is sized 1:1 to the vessel. Available sizes are 2.5 to 4 mm. The balloons are bulkier than equivalent noncompliant balloons so lesion preparation with non-compliant or cutting balloons may be required to enable IVL balloon delivery. In some circumstances, initial RA may be necessary to create a channel to facilitate subsequent IVL. When the IVL balloon is delivered to the target lesion, it is inflated to 4 atm, and 10 pulses of sonic waves are delivered, one pulse per second. The balloon is then expanded to 6 atm to test for full expansion as a marker of successful lesion modification. Each balloon may be used for a total of 80 pulses, delivered in 10-pulse trains. The balloon can be deflated between 10-pulse treatments to prevent prolonged ischemia if required. At least two 10-pulse cycles are recommended for each area of treatment. The standard balloon is 12 mm in length, and for longer lesions, the balloon is repositioned sequentially across the lesion to enable pulse delivery across the whole lesion length.

Intravascular lithotripsy is currently only licensed for treatment of calcification in native coronary arteries. However, off-license use for treatment of under expanded stents is an area of interest because it addresses deeper calcification beneath the stent that is not accessible via rotablation.

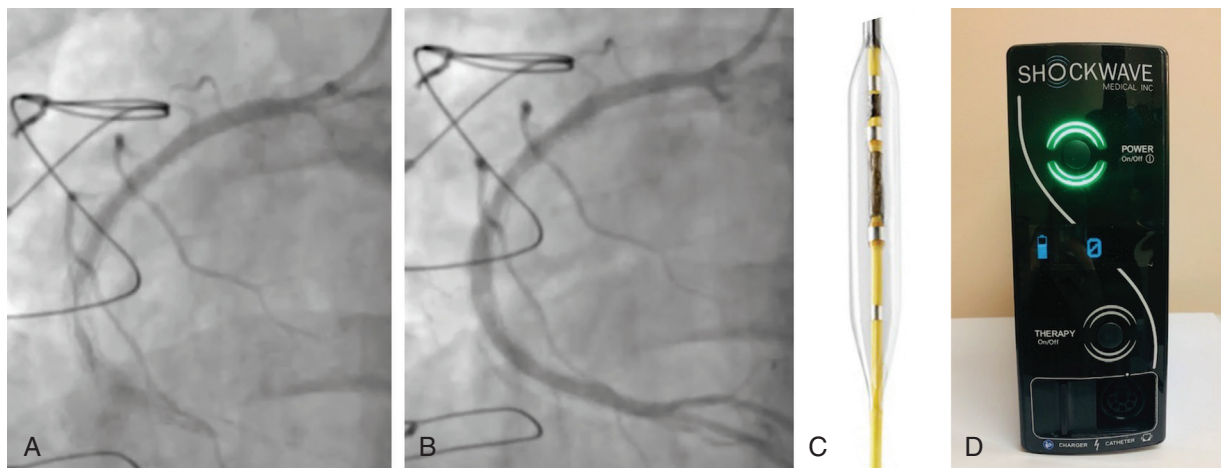


FIGURE 12.8 Intravascular lithotripsy (IVL). **A**, Preprocedure right coronary artery with severe calcification and in-stent restenosis. **B**, Results of IVL followed by stent implantation. **C**, The IVL console. **D**, The IVL balloon.

TABLE 12.7 Trials of Intravascular Lithotripsy

STUDY	STUDY DESIGN	PATIENTS (n)	PRIMARY ENDPOINT	RESULTS
Disrupt CAD I (Brinton et al. ²⁵)	- Design: prospective, multicenter, single arm - Inclusion: patients with ≥ 1 lesion requiring PCI $\geq 50\%$ diameter stenosis, length ≤ 32 mm, and heavy calcification assessed angiographically	60	- Primary endpoint: clinical success, defined as the ability of IVL to produce a residual diameter stenosis $< 50\%$ after stenting with no evidence of in-hospital MACE (cardiac death, MI, or TVR) - Primary safety endpoint: freedom from MACE at 30 days; data also collected at 6 mo	- Primary endpoint: 95% clinical success; three periprocedural MIs; no unresolved dissections, slow-flow or no-flow, embolization, or perforations - Primary safety endpoint: MACE 8.3% at 6 mo; two cardiac deaths adjudicated as unlikely related to IVL; no new MIs or TVRs
Disrupt CAD II (Ali et al. ²⁶)	- Design: prospective multicenter, single-arm post-approval study - Inclusion: patients with stable, unstable, or silent ischemia and severely calcified de novo coronary artery lesions undergoing PCI with a single target lesion $\geq 50\%$ diameter stenosis, length ≤ 32 mm	120	- Primary endpoint: in-hospital MACEs (cardiac death, MI, or TVR) - OCT substudy: to evaluate the mechanism of action of IVL	- Primary endpoint: 5.8% of patients: 7 non-Q-wave MIs; no procedural abrupt closure, slow or no reflow, or perforations - OCT substudy (47 patients): calcium fracture identified in 78.7% of lesions with 3.4 ± 2.6 fractures per lesion, measuring 5.5 ± 5.0 mm in length.
Disrupt CAD III (Hill et al. ²⁷)	- Design: Prospective single arm unblinded study for FDA regulatory approval - Inclusion: patients with stable, unstable, or silent ischemia and severely calcified de novo coronary artery lesions undergoing PCI	431	Primary endpoint; 30-day freedom from MACE (cardiac death, MI, TVR)	92% freedom from major adverse events; met prespecified safety criteria; OCT substudy (98 patients) showed longitudinal calcium fractures after IVL in 67% of lesions

FDA, Food and Drug Administration; IVL, intravascular lithotripsy; MACE, major adverse cardiac event; MI, myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

Clinical Studies of Intravascular Lithotripsy

There have been three trials of intracoronary IVL (Disrupt coronary artery disease [CAD] I, II, and III). These are summarized in Table 12.7. Taken together, the trials demonstrated high rates of procedural success with low rates of procedural complications.

In DISRUPT CAD III, 30-day the major adverse cardiovascular event rate was 7.8%.²⁷ This compares favorably with the 8% rate of major cardiovascular adverse events in evaluate the safety and efficacy of OAS in treating severely calcified coronary lesions (ORBIT) 1¹³ and 10% in ORBIT II,¹⁴ although no randomized data are available to compare IVL with other calcium modification techniques.

CONCLUSIONS

Calcified coronary lesions are an often encountered and challenging situation for interventional cardiologists. Various devices for plaque modification before stent deploy-

ment have been developed, all with efficacy and safety in appropriate anatomy. Choice of modality is guided by operator comfort and preference, device availability, specific lesion characteristics, and patient-specific factors, including hemodynamic stability. Algorithms have been proposed for choice of modality depending on lesion characteristics (Figure 12.9), with IVL recommended as first line for 360-degree circumferential calcification and deep wall calcium, scoring balloons for short lesions of 180-degree circumference, RA or OA for nodular calcification, and laser or rota for balloon uncrossable lesions.²⁸ Significant vessel tortuosity is considered a relative contraindication to atherectomy caused by increased risks of vessel trauma and may favor use of balloon angioplasty based plaque modification. Most important, when significant calcium is seen either fluoroscopically or via intravascular imaging, strong consideration should be given to pretreatment with one of the available devices to ensure appropriate stent expansion and improve short- and long-term procedural success rates.

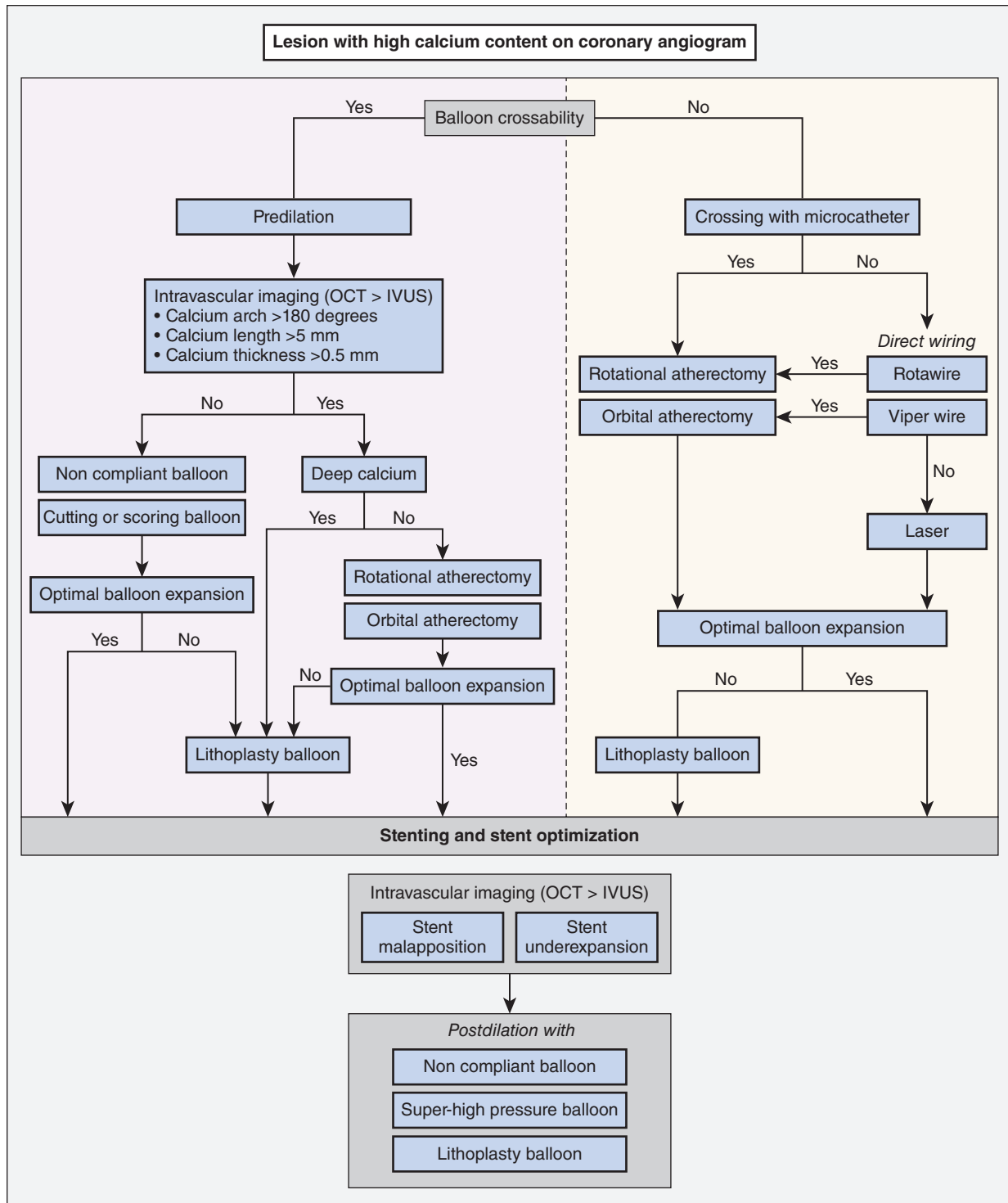


FIGURE 12.9 Algorithm for choice of calcium modification modality based on lesion characteristics. *IVUS*, Intravascular ultrasonography; *OCT*, optical coherence tomography. (Reproduced from De Maria GL, Scarsini R, Banning AP. Management of calcified coronary artery lesions: is it time to change our interventional therapeutic approach? *JACC Cardiovasc Interv.* 2019;12:1465-1478.)

REFERENCES

1. Genereux P, Madhavan MV, Mintz GS, et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes: pooled analysis from the HORIZONS-AMI and ACUTY trials. *J Am Coll Cardiol.* 2014;63(18):1845-1854.
2. Hsu JT, Kyo E, Chu CM, et al. Impact of calcification length ratio on the intervention for chronic total occlusions. *Int J Cardiol.* 2011;150:135-141.
3. Virmani R, Farb A, Burke AP. Coronary angioplasty from the perspective of atherosclerotic plaque: morphologic predictors of immediate success and restenosis. *Am Heart J.* 1994;127:163-179.
4. Shiode N, Kozuma K, Aoki J, et al. The impact of coronary calcification on angiographic and 3-year clinical outcomes of everolimus-eluting stents: results of a XIENCE V/PROMUS postmarketing surveillance study. *Cardiovasc Interv Ther.* 2018;33:313-320.
5. Kuntz RE, Safian RD, Carrozza JP, et al. The importance of acute luminal diameter in determining restenosis after coronary atherectomy or stenting. *Circulation.* 1992;86:1827-1835.
6. Abdel-Wahab M, Toelg R, Byrne RA, et al. High-Speed rotational atherectomy versus modified balloons prior to drug-eluting stent implantation in severely calcified coronary lesions. *Circ Cardiovasc Interv.* 2018;11(10):e007415.



7. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:2574-2609.
8. Reifart N, Vandormael M, Krajcar M, et al. Randomized comparison of angioplasty of complex coronary lesions at a single center. Excimer Laser, Rotational Atherectomy, and Balloon Angioplasty Comparison (ERBAC) Study. *Circulation*. 1997;96:91-98.
9. Dietz U, Rupprecht HJ, Ekin O, et al. Angiographic analysis of immediate and long-term results of PTCA vs. PTCA in complex lesions (COBRA study). *Catheter Cardiovasc Interv*. 2001;53:359-367.
10. Safian RD, Feldman T, Muller DW, et al. Coronary Angioplasty and Rotational Atherectomy Trial (CARAT): immediate and late results of a prospective multicenter randomized trial. *Catheter Cardiovasc Interv*. 2001;53:213-220.
11. Whitlow PL, Bass TA, Kipperman RM, et al. Results of the study to determine rotablator and transluminal angioplasty strategy (STRATAS). *Am J Cardiol*. 2001;87:699-705.
12. Abdel-Wahab M, Richardt G, Joachim Buttner H, et al. High-speed rotational atherectomy before paclitaxel-eluting stent implantation in complex calcified coronary lesions: the randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) trial. *JACC Cardiovasc Interv*. 2013;6:10-19.
13. Parikh K, Chandra P, Choksi N, et al. Safety and feasibility of orbital atherectomy for the treatment of calcified coronary lesions: the ORBIT I trial. *Catheter Cardiovasc Interv*. 2013;81:1134-1139.
14. Chambers JW, Feldman RL, Himmelstein SI, et al. Pivotal trial to evaluate the safety and efficacy of the orbital atherectomy system in treating de novo, severely calcified coronary lesions (ORBIT II). *JACC Cardiovasc Interv*. 2014;7:510-518.
15. Redfors B, Sharma SK, Saito S, et al. Novel micro crown orbital atherectomy for severe lesion calcification: Coronary Orbital Atherectomy System Study (COAST). *Circ Cardiovasc Interv*. 2020;13(8):e008993.
16. Hara H, Nakamura M, Asahara T, et al. Intravascular ultrasonic comparisons of mechanisms of vasodilatation of cutting balloon angioplasty versus conventional balloon angioplasty. *Am J Cardiol*. 2002;89:1253-1256.
17. Mauri L, Bonan R, Weiner BH, et al. Cutting balloon angioplasty for the prevention of restenosis: results of the Cutting Balloon Global Randomized Trial. *Am J Cardiol*. 2002;90:1079-1083.
18. de Ribamar Costa J Jr, Mintz GS, Carlier SG, et al. Nonrandomized comparison of coronary stenting under intravascular ultrasound guidance of direct stenting without predilation versus conventional predilation with a semi-compliant balloon versus predilation with a new scoring balloon. *Am J Cardiol*. 2007;100:812-817.
19. Sonoda S, Morino Y, Ako J, et al. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the SIRIUS trial. *J Am Coll Cardiol*. 2004;43:1959-1963.
20. Ozaki Y, Yamaguchi T, Suzuki T, et al. Impact of cutting balloon angioplasty (CBA) prior to bare metal stenting on restenosis. *Circ J*. 2007;71(1):1-8.
21. Rawlins J, Din JN, Talwar S, O'Kane P. Coronary intervention with the excimer laser: review of the technology and outcome data. *Interv Cardiol*. 2016;11(1):27-32.
22. Appelman YEA, Piek JJ, Strikwerda S, et al. Randomised trial of excimer laser angioplasty versus balloon angioplasty for treatment of obstructive coronary artery disease. *Lancet*. 1996;347:79-84.
23. Stone GW, de Marchena E, Dageforde D, et al. Prospective, randomized, multicenter comparison of laser-facilitated balloon angioplasty versus stand-alone balloon angioplasty in patients with obstructive coronary artery disease. The Laser Angioplasty Versus Angioplasty (LAVA) Trial Investigators. *J Am Coll Cardiol*. 1997;30:1714-1721.
24. Latib A, Takagi K, Chizzola G, et al. Excimer Laser LEsion modification to expand non-dilatable stents: the ELLEMENT registry. *Cardiovasc Revasc Med*. 2014;15:8-12.
25. Brinton TJ, Ali ZA, Hill JM, et al. Feasibility of shockwave coronary intravascular lithotripsy for the treatment of calcified coronary stenoses. *Circulation*. 2019;139:834-836.
26. Ali ZA, Nef H, Escaned J, et al. Safety and effectiveness of coronary intravascular lithotripsy for treatment of severely calcified coronary stenoses: the Disrupt CAD II study. *Circ Cardiovasc Interv*. 2019;12(10):e008434.
27. Hill JM, Kereiakes DJ, Shlofmitz RA, et al. Intravascular lithotripsy for treatment of severely calcified coronary artery disease. *J Am Coll Cardiol*. 2020;76(22):2635-2646.
28. De Maria GL, Scarsini R, Banning AP. Management of calcific coronary artery lesions: is it time to change our interventional therapeutic approach? *JACC Cardiovasc Interv*. 2019;12:1465-1478.



13 Treatment Of In-Stent Restenosis

J.J. COUGHLAN, ROBERT A. BYRNE, FERNANDO ALFONSO AND ADNAN KASTRATI

INTRODUCTION, 235

DEFINITION, 235

DIAGNOSIS, 236

PATHOPHYSIOLOGY, 236

MECHANISMS, 236

Clinical Presentation, 237

Angiographic Classification, 237

INTRAVASCULAR IMAGING, 237

Optical Coherence Tomography, 239

Intravascular Ultrasonography, 240

Correlation Between Imaging and Histology, 240

Intracoronary Physiology, 240

TREATMENT, 241

General Principles, 241

Evidence Base for In-Stent Restenosis

Treatment and Systematic Review

Methods, 241

Balloon Angioplasty, 241

Bare-Metal Stenting, 248

Intravascular Brachytherapy, 248

Rotational Atherectomy, 248

CUTTING AND SCORING BALLOONS, 248

Adjunctive Medical Therapy, 249

Drug-Eluting Stent Implantation, 249

DES Strategy: Hetero-DES versus

Homo-DES, 249

Drug-Coated Balloons, 249

Paclitaxel Drug-Coated Balloons, 252

Sirolimus Drug-Coated Balloons, 252

Drug-Coated Balloons: The Importance of Lesion Preparation, 252

Drug-Eluting Stents versus Drug-Coated Balloons for the Treatment of In-Stent Restenosis: Direct Evidence, 252

Bioresorbable Scaffolds, 252

Excimer Coronary Laser Atherectomy, 252

Intravascular Lithotripsy, 253

Coronary Artery Bypass Grafting, 253

TREATMENT ALGORITHM, 253

FUTURE INTERVENTIONAL PARADIGMS, 254

CONCLUSIONS, 254

INTRODUCTION

This chapter discusses the management of in-stent restenosis (ISR). ISR refers to a reduction in the luminal diameter of a stent after successful percutaneous coronary intervention (PCI) (Figure 13.1) and is the most common cause of stent failure.^{1,2} Drug-eluting stents (DESs) have reduced the incidence of ISR compared with bare-metal stents (BMSs).^{3,4} However, contemporary series suggest that ISR PCI procedures still account for around 1 in 10 of all PCI procedures performed in modern interventional practice.^{5,6} One potential explanation for this is that the improved clinical efficacy observed with DES has coincided with an expansion of PCI to increasingly complex lesion and patient subsets. As a result, while ISR rates have been reduced in relative terms, the absolute number of ISR cases requiring management remains considerable. In addition, although rates of ISR at 1 year after DES implantation are low, most patients undergoing stenting have considerable remaining life expectancy, and rates continue to accumulate with time, such that at 10 years, about one in five patients may develop ISR.⁷ The management of ISR is recognized to be challenging, with high rates of recurrence at medium- to long-term follow-up.^{8,9} ISR can also frequently present clinically as an acute coronary syndrome (ACS), with associated morbidity and mortality.^{5,10} Therefore, the development of strategies to prevent and optimally manage ISR is an important challenge for interventional cardiologists, with the potential to improve patient outcomes and to reduce morbidity and mortality.

DEFINITION

ISR is defined as a reduction in the luminal diameter of a stent after successful PCI. Angiographically, ISR is



FIGURE 13.1 Focal recurrent in-stent restenosis (ISR) 4 years after drug-eluting stent implantation for ISR in the proximal right coronary artery (Video 13.1). The restenotic lesion was predilated with a noncompliant balloon and treated with a 60-second drug-coated balloon inflation with good acute angiographic result (Video 13.2). Repeat angiography 7 months later shows an excellent result (Video 13.3).

defined as a recurrent reduction in diameter of 50% or greater within the stented segment or the stent edges (the stent edges are defined as the vessel segments 5 mm proximal and distal to the stent).¹¹ An angiographic example of ISR is shown in Figure 13.1. On intravascular imaging (IVI), ISR is defined as a reduction of 75% or more of the vessel area in cross-section.¹² Autopsy studies use



a similar definition for ISR, defining it as a pathological vessel renarrowing measuring greater than 75% of the reference vessel area in cross-section.^{13,14}

These definitions are binary, classifying the presence or absence of ISR as per an arbitrary restenosis value. However, ISR can perhaps better be regarded as a pathophysiological continuum. Accordingly, continuous parameters reflecting the degree of luminal narrowing after stenting may also be useful. These parameters include percentage diameter stenosis at follow-up angiography, minimal lumen diameter (MLD) at follow-up, and late lumen loss (LLL). LLL is defined as the difference between the MLD immediately after the procedure and the MLD at follow-up angiography. This continuous pathophysiological approach may be better suited for comparisons of the relative antirestenotic efficacy of stent- and balloon-based treatment modalities.

DIAGNOSIS

Although the diagnosis of ISR may be inferred from clinical findings and the results of noninvasive imaging, the diagnosis of ISR in living patients is usually based on the angiographic or IVI definitions outlined in the previous section. Multiple diagnostic modalities can be used to make the diagnosis and often provide complementary information to guide management. An intrinsic limitation of coronary angiography is that it is a two-dimensional representation of a three-dimensional process. IVI can provide important additional information in three dimensions to define and classify ISR. This can be useful not only to more accurately define ISR severity, but also to identify the underlying mechanisms of the ISR. Noninvasive computed tomography coronary angiography is not widely used to make a definitive diagnosis of ISR because of issues with spatial resolution and metal-related artifacts.¹⁵ It is also important to consider that not all ISR will result in clinical signs or symptoms of ischemia. This is sometimes referred to as *silent restenosis*.

PATHOPHYSIOLOGY

Restenosis can occur as a result of several distinct pathophysiological processes,¹⁶ including prolapse of the disrupted plaque, elastic recoil of the vessel wall, and constrictive vascular remodeling. However, ISR after stenting is usually caused by neointimal hyperplasia (caused by extracellular matrix deposition and vascular smooth muscle cell hyperplasia), de novo in-stent atherosclerosis (neoatherosclerosis), or a combination of both. In occasional cases of ISR early after stenting with DES, a hypocellular proteoglycan-rich neointimal tissue can be seen.

When treating patients with obstructive coronary artery disease (CAD), stent implantation causes additional vessel injury compared to balloon angioplasty (BA) alone, which serves as a stimulus for neointimal tissue formation during vessel healing. The term *neointimal hyperplasia* is used to describe the accumulation of vascular smooth

muscle cells and extracellular matrix in the intima. The term *neoatherosclerosis* is used to describe the accumulation of lipid-laden foamy macrophages with or without necrotic core formation or calcification within the neointima.^{17,18} DESs have reduced the incidence of early restenosis compared with the BMS era, but the delayed vessel healing associated with DES may contribute to an increased incidence and accelerated course of de novo atherosclerotic disease within the stent in the months and years after intervention.¹⁷

There appear to be some differences between ISR after BMS and DES implantation.¹⁹ These include differences with regard to angiographic appearances, the time course of luminal narrowing, morphologic appearances at IVI, histopathology, and clinical response to interventions.^{14,17,19,20} These factors are summarized in Table 13.1.

Although several studies have reported that neointimal hyperplasia is encountered more frequently in BMS ISR and neoatherosclerosis is more common in DES ISR, this may be an oversimplification. The underlying ISR pathology may relate not only to the underlying stent type, but also to the time course of ISR development after PCI. For example, optical coherence tomography (OCT) findings suggestive of neoatherosclerosis are identified less commonly in DES ISR that develops within the first year after PCI (early DES ISR) compared with DES ISR that develops beyond 1 year after PCI (late DES ISR).²¹⁻²³ Neoatherosclerotic ISR appears to develop in tandem with native atherosclerotic disease progression, suggesting similar underlying pathophysiological mechanisms, albeit with an accelerated course in neoatherosclerosis.²⁴

Angiographic surveillance studies suggest that while BMS ISR peaks within the first year after stent implantation, DES ISR continues to increase steadily for several years after PCI.²⁵⁻²⁸ This may have relevance for patient follow-up. It is also important to consider that the observed incidence of ISR will be dependent on the nature of the clinical follow-up, with routine angiographic surveillance likely to result in increased identification of “silent” ISR.

MECHANISMS

It is important to recognize that rather than reflecting a specific pathophysiological entity, ISR is a broad term that represents a final common pathway that may be related to a number of underlying mechanical issues and pathophysiological processes. Several contributory mechanisms and pathophysiological processes may coexist simultaneously in an ISR case,²⁰ and all should be identified and addressed if possible during the ISR therapeutic procedure.²⁹

Potential mechanical or technical factors associated with ISR include stent undersizing, stent underexpansion, vessel calcification, stent fracture, and geographic miss.^{30,31} Biological mechanisms of ISR include neointimal hyperplasia and neoatherosclerosis.¹⁹ These may occur as a result of a lack of antiproliferative agent effect, vessel toxicity, or vessel hypersensitivity.

One potentially useful paradigm when managing ISR is to consider that ISR may occur as a result of a combination

TABLE 13.1 Comparison of the Principal Imaging and Histologic Features of Restenotic Tissue After Drug-Eluting Stent and Bare-Metal Stent Implantation

	BARE-METAL STENT RESTENOSIS	DRUG-ELUTING STENT RESTENOSIS
Imaging Features		
Angiographic morphology	Diffuse pattern more common	Focal pattern more common
OCT tissue properties	Homogenous, high signal band most common	Layered structure or heterogenous most common
Time course of late luminal loss	Late loss maximal by 6–8 mo	Ongoing late loss out to 5 y
Histopathologic Features		
Smooth muscle cellularity	Rich	Hypocellular
Proteoglycan content	Moderate	High
Peristut fibrin and inflammation	Occasional	Frequent
Complete endothelialisation	3–6 mo	≤48 mo
Thrombus present	Occasional	Occasional
Neoatherosclerosis	Relatively infrequent, late	Relatively frequent, accelerated course

OCT, Optical coherence tomography.

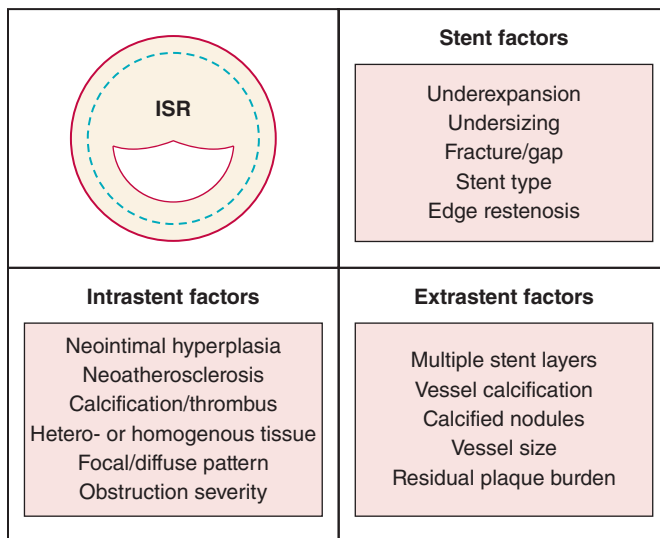


FIGURE 13.2 Factors to consider when performing in-stent restenosis (ISR) percutaneous coronary intervention (PCI). ISR may be attributed to a variable degree of influence of three categories of factors in the stented coronary artery: extrastent factors, stent-related factors, or intrastent factors. Adapted from: Alfonso et al.³²

of three categories of factors in the stented coronary artery: extrastent factors (i.e., factors that prevent adequate stent expansion), stent-related factors (i.e., stent undersizing, stent fracture), or intrastent factors (i.e., excessive tissue proliferation within the stent). This paradigm is summarized in Figure 13.2.

A study analyzing data from intravascular ultrasonography (IVUS) acquisitions reported that in BMS ISR and DES ISR lesions, the majority of patients had dominant neointimal hyperplasia.²⁰ In the same study, 40% of second-generation DES ISR lesions had a stent cross sectional area of less than 5 mm², and 66% had more than 50% neointimal hyperplasia, indicating that both stent underexpansion and neointimal hyperplasia are commonly encountered in second-generation DES ISR.^{20,33} However, a limitation of this study is that it did not evaluate the frequency of neoatherosclerotic ISR.

Clinical Presentation

In-stent restenosis can commonly present as an ACS,³⁴ with a similar proportion of ACS presentations in DES and BMS ISR.³⁵ ACS presentation has been associated with a higher risk of recurrent adverse cardiovascular events and angiographic restenosis after ISR PCI.³⁵ IVI has demonstrated acute plaque rupture and stent thrombosis in patients presenting with ISR, providing novel insights into the link between ISR and ACS. This has led to an increased appreciation that these pathologies can be considered part of the ISR presentation spectrum, with neoatherosclerosis potentially representing the common link between what were previously considered separate clinical entities (Figure 13.3).

Angiographic Classification

A widely adopted angiographic ISR classification was proposed by Mehran et al.³⁶ in a manuscript from the BMS era. This classified patients with BMS ISR into four groups: type I, focal; type II, diffuse, within stent; type III, diffuse, within and beyond stent; and type IV, occlusive (see case examples in Videos 13.8 to 13.22).

Although widely used, the Mehran classification is not without limitations. These include that it may not be as relevant for DES ISR, in which a greater proportion of ISR is focal,³⁷ and that the classification is based only on angiographic appearances and therefore provides no information about underlying pathophysiological mechanisms or the presence or absence of mechanical factors. The future development of novel ISR classification systems tailored to the DES era may be useful.

INTRAVASCULAR IMAGING

OCT and IVUS are the two most commonly used forms of IVI in clinical practice. The use of IVI to assess and manage ISR is recommended by expert consensus and guidelines (Class IIa, Level C).³⁸ IVI allows the operator to more

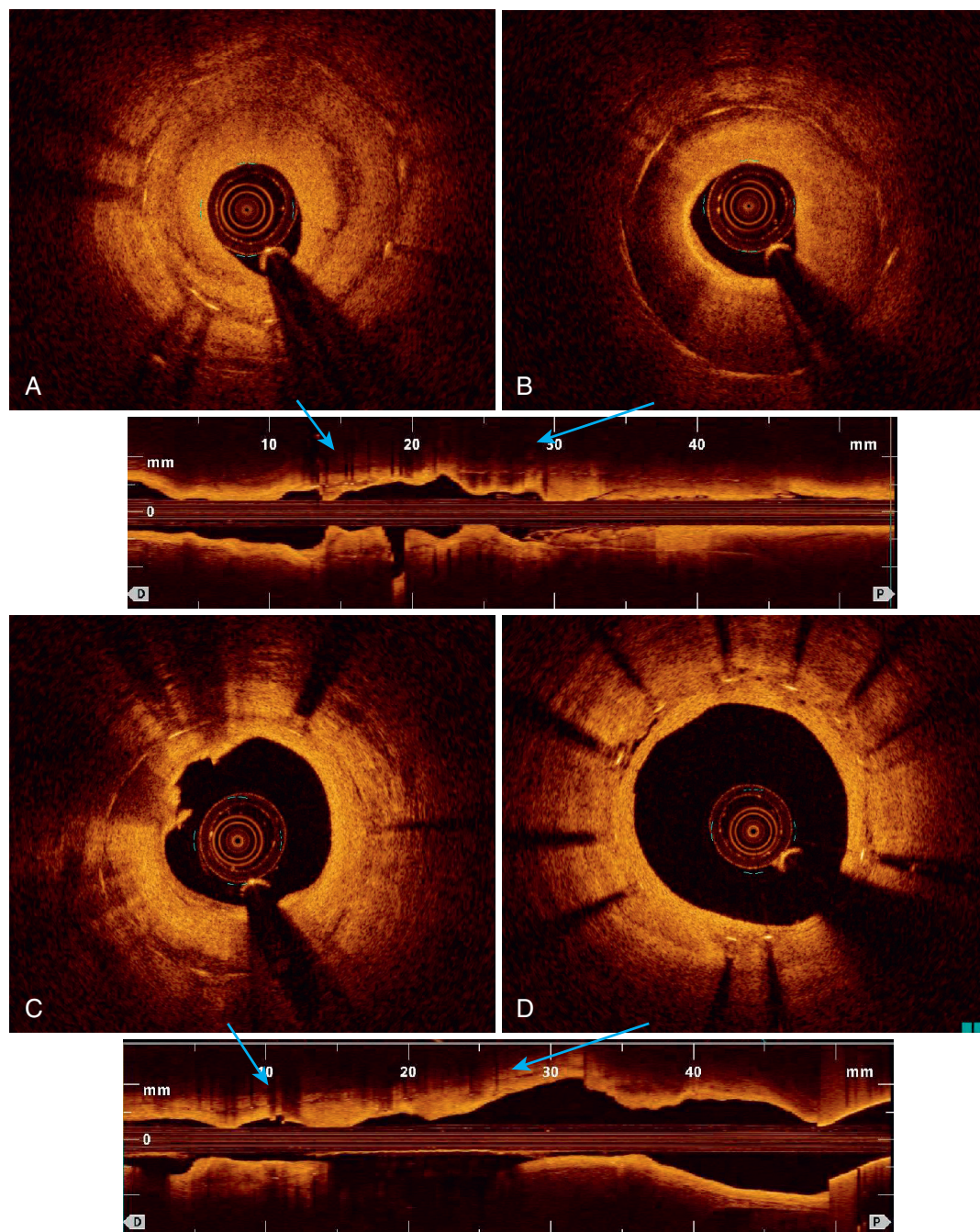


FIGURE 13.3 Diffuse in-stent restenosis (ISR) showing features of in-stent neoatherosclerosis by optical coherence tomography. ISR 9 years after long-segment drug-eluting stent implantation showing features of in-stent neoatherosclerosis. Angiography shows diffuse ISR (Video 13.4). Optical coherence tomography shows a distal high-grade layered pattern of ISR (A) with an area of attenuated signal intensity 10 to 15 mm more proximally (B), which likely represents lipid-core atherosclerotic plaque. More proximally still, an area of possible in-stent plaque erosion/rupture is visible (C; at the 10 o'clock position). The proximal stent edge is free of restenosis, with a thin layer of neointima covering the stent struts (D). Punctate areas of low signal intensity likely represent neovascularization. Predilation with noncompliant balloon angioplasty, treatment with a drug-coated balloon (Video 13.5) and additional distal stent implantation (Video 13.6) resulted in a satisfactory acute appearance (Video 13.7).

accurately quantify the degree of ISR and to identify underlying pathophysiological mechanisms.^{20,30,39} In addition, IVI may resolve diagnostic uncertainty when it is unclear from angiography whether or not the luminal narrowing is within the body of the stent or beyond its edges. However, there are currently limited data to support the hypothesis that the use of IVI leads to improved outcomes in the management of ISR. It is important to

acknowledge that there are currently no randomized data supporting the guidance of ISR management based on different patterns of IVI appearance, and this represents a gap in scientific knowledge. In fact, the majority of randomized controlled trials (RCTs) on the management of ISR did not mandate the use of IVI when performing ISR PCI, and the use of IVI in clinical practice is known to be variable.⁴⁰

Optical Coherence Tomography

Optical coherence tomography provides superior spatial resolution to IVUS. This allows the operator to characterize the neointimal tissue in more detail.^{19,41} However, limitations of OCT include the need to use contrast media to obtain a blood-free field for image acquisition and reduced tissue penetration compared with IVUS. The need for additional contrast media may be of particular concern in patients with renal dysfunction because of the increased risk of nephrotoxicity. Because of reduced tissue penetration with OCT, the external elastic lamina (EEL) cannot always be clearly identified, and this can make accurate vessel sizing challenging.

Using OCT,⁴² ISR can be classified into four groups based on the tissue appearance:

- **Homogeneous:** uniform high signal intensity, low backscatter, typical of areas of high smooth muscle cell content
- **Heterogeneous:** mixed signal intensity; may represent proteoglycan-rich neointima or early neoatherosclerotic plaque
- **Attenuated:** superficial high signal intensity, high backscatter, likely indicative of lipid-core plaque

- **Layered:** superficial high signal intensity with deep low signal intensity, often in peristrut areas

Examples of ISR tissue patterns on OCT are shown in [Figure 13.4](#). A homogeneous tissue pattern on OCT imaging was often considered characteristic of BMS ISR, which tends to occur relatively early after PCI (i.e., within the first year). The other three patterns (attenuated, layered, and heterogeneous) are generally considered to represent different parts of the neoatherosclerotic disease spectrum, which has traditionally been more associated with DES ISR.⁴² However, as mentioned earlier, all four tissue patterns have been identified in both DES ISR and BMS ISR, and their relative prevalences may be impacted by the timing of the ISR occurrence and assessment. In very late BMS ISR, occurring more than 5 years after stent implantation, a heterogeneous tissue pattern has been reported to be more common.⁴³ Similarly for DES ISR, findings corresponding to neoatherosclerosis on OCT become more common with increasing durations of follow-up after the initial stent implantation.^{21,22} It is also important to consider that these OCT tissue patterns are not necessarily mutually exclusive, and the observed tissue pattern may vary throughout the restenosed stent.

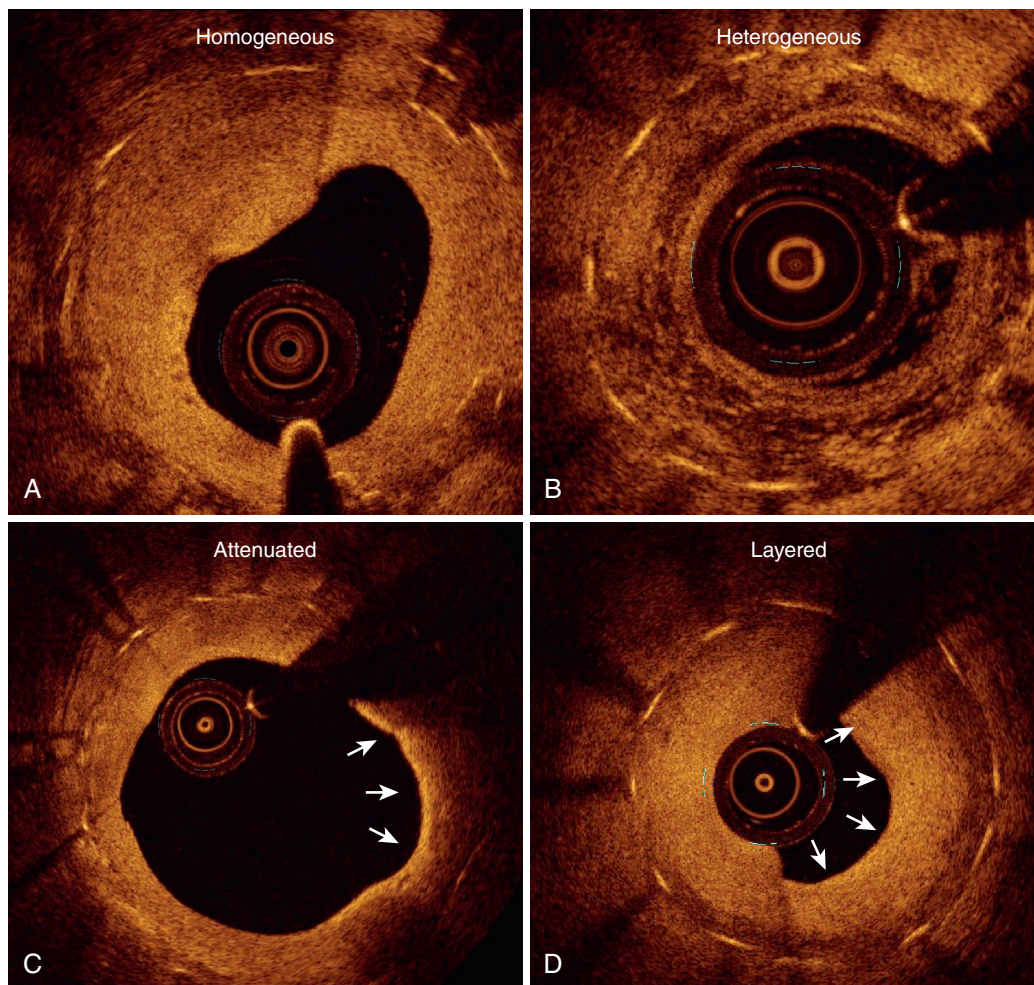


FIGURE 13.4 Classification of tissue types by optical coherence tomography in patients with in-stent restenosis. Restenotic tissue types are usually classified into four categories: homogeneous—uniform high signal intensity (**A**); heterogeneous—variable signal intensity (**B**); attenuated—typical features between the 2 and 5 o'clock positions with superficial high signal intensity (*white arrows*), rapid signal attenuation, and high backscatter (**C**); and layered—superficial high signal intensity and deep low signal intensity in peristrut areas (**D**).

Intravascular Ultrasonography

Compared with OCT, IVUS has some advantages, including deeper tissue penetration and no requirement for a blood-free field. However, detailed tissue characterization to the same degree as OCT is not possible. Despite this limitation, IVUS can still demonstrate several findings relevant to ISR, including neointimal hyperplasia, mature neoatherosclerosis, stent underexpansion, stent undersizing, and vessel calcification.^{20,30} In addition, given that the EEL is usually well delineated, accurate vessel sizing is facilitated.

Correlation Between Imaging and Histology

The tissue appearance of ISR identified on IVI can be considered to be representative of the underlying histopathology. A homogenous tissue appearance on OCT has

been shown to correspond to fibrous connective tissue with cell-rich neointima and heterogeneous OCT tissue patterns are associated with increased fibrin deposition and loose connective tissue.⁴⁴ In addition, lipid pools are frequently detected, showing the characteristic pattern of neoatherosclerosis. Guiding the ISR therapeutic approach based on IVI findings has not been assessed in a randomized trial.⁴⁵ Examples of some of the histopathological features of BMS and DES ISR are demonstrated in Figure 13.5.

Intracoronary Physiology

There are limited data on the use of intracoronary physiology (e.g., fractional flow reserve [FFR], instantaneous wave-free ratio) for the assessment of ISR. However, determining the physiological significance of an ISR lesion

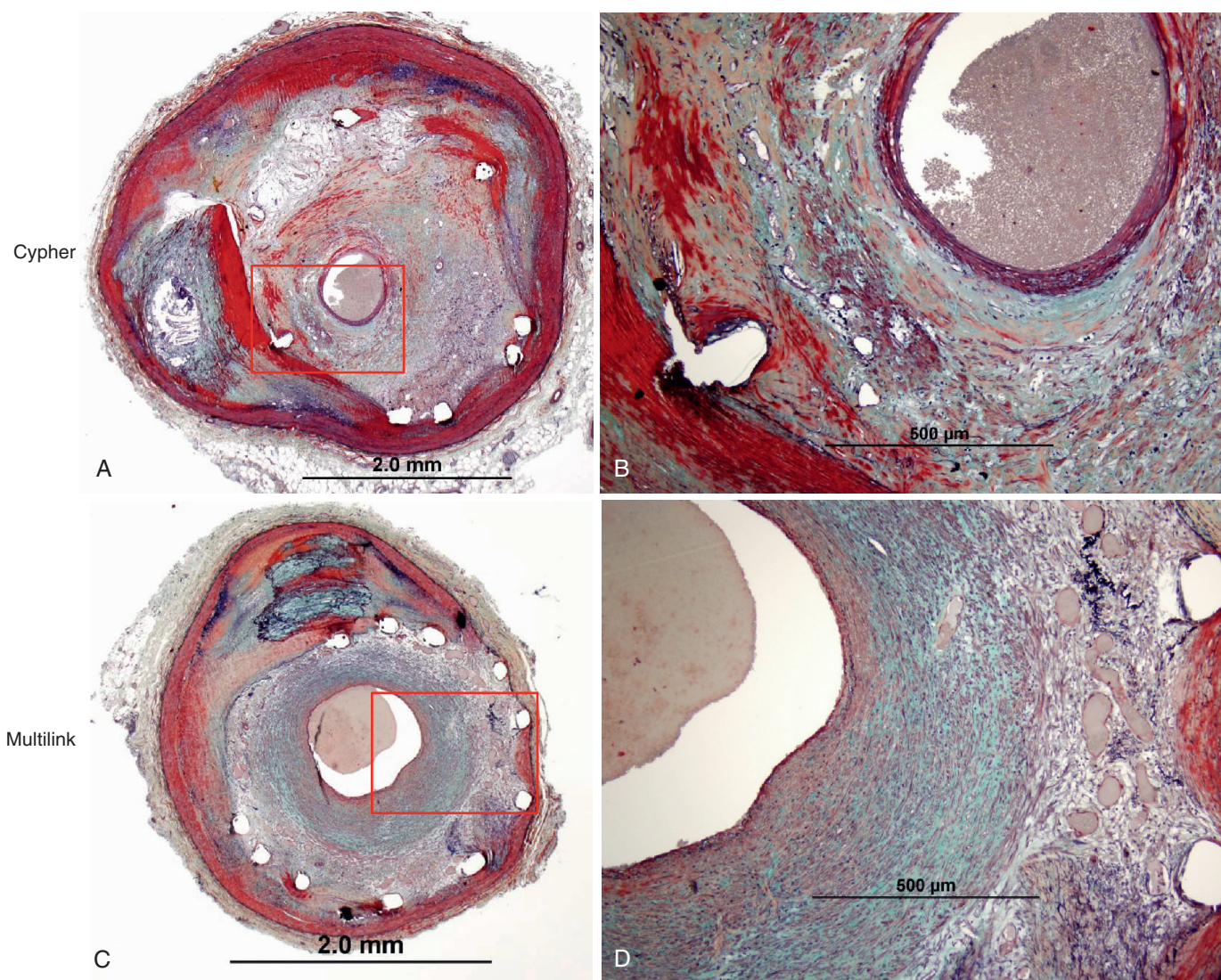


FIGURE 13.5 Histopathology of restenosis in drug-eluting and bare-metal stents. Low-power (2.5 $\times$) magnification of a Movat Pentachrome-stained section of a Cypher sirolimus-eluting stent (A) showing severe in-stent restenosis (ISR) with almost complete occlusion. There is postmortem clot in the lumen. Higher magnification (10 $\times$) section shows a stent strut with surrounding proteoglycan-rich neointimal tissue and the presence of foam cells and neovascularization (B). Low-power (2.5 $\times$) magnification of a Multilink bare-metal stent (C) with severe ISR and (D) high-power (10 $\times$) magnification shows a predominance of smooth muscle cells with neovascularization and chronic inflammation in the surrounding stent struts.

might be considered as an adjunctive measure to assist clinical decision making, particularly in patients with ISR of intermediate angiographic severity.³⁴ A study with 1 year follow-up has suggested that PCI can be deferred safely in angiographically moderate ISR lesions with a FFR value of 0.75 or more.⁴⁶ Although there are no dedicated randomized trials supporting an FFR-guided ISR treatment strategy, there is little reason to believe that these data from large-scale trials of intracoronary physiology-guidance in patients considered for PCI are not generalizable to patients presenting with ISR.

TREATMENT

General Principles

Patients with ISR should be assessed according to the same diagnostic pathway as patients with de novo CAD. Similar to de novo CAD, symptoms or documented ischemia associated with the ISR lesion should be demonstrated before proceeding with repeat revascularization. First and foremost, these patients deserve careful evaluation of their cardiovascular risk profile. This is important to ensure the implementation of well-established general measures for the reduction of cardiovascular risk, including the optimization of medical treatment, and should follow the guideline recommendations for secondary prevention in CAD. In patients with an indication for repeat revascularization, both surgical and repeat percutaneous revascularization may be considered. Because the majority of ISR in contemporary practice is focal in morphology, repeat PCI is the most common approach.

In patients undergoing PCI for ISR, the basic tenet of intervention is that efficacy is optimized by maximizing acute gain and minimizing late loss (Figure 13.6). The major difference with PCI for ISR in comparison with de novo lesions is the presence of an existing stent scaffold in the diseased coronary segment. This may offer certain mechanical advantages if the structural integrity of the stent is intact, but can also provide a challenge if the original stent was underexpanded.³¹ It is particularly important that persistent issues leading to the original stent

failure are identified and addressed to minimize the chance of future recurrence. It is also important to identify patients with edge restenosis, which may be related to incomplete lesion coverage at the time of the index PCI, and for which repeat stenting will usually be preferred.

For ISR treated with DES implantation, underexpansion of the restenosed stent (the primary stent) is associated with an increased risk of postprocedural secondary stent underexpansion, major adverse cardiac events, and ISR recurrence.^{30,31} Postprocedural stent underexpansion has also been shown to predict ISR recurrence after ISR treatment with drug-coated balloons (DCBs).⁴⁷ These data indicate that failure to impact on the underlying mechanisms of ISR increases the future risk of recurrence. Indeed, suboptimal treatment of ISR can not only increase the likelihood of clinical recurrence, but can also result in the management of these recurrences being more difficult. Comprehensively identifying and addressing mechanical factors contributing to ISR before ISR PCI may help to avoid this.

Evidence Base for In-Stent Restenosis Treatment and Systematic Review Methods

Numerous RCTs have been performed in patients with ISR, and a wide range of therapeutic approaches have been assessed (Figure 13.7). When these treatments have been compared using network meta-analysis, DES implantation and DCB therapy have consistently emerged as the best approaches for the treatment of ISR.^{48,49}

We performed a systematic review of the literature at the time of the writing of this chapter to identify trials comparing treatment modalities or strategies for ISR. RCTs comparing therapeutic modalities in patients with coronary ISR are included in Table 13.2, Table 13.3, and Figure 13.7. In the next sections of this chapter, we will discuss the treatment options for ISR in the chronological order in which they were assessed in randomized clinical trials (see Figure 13.7).

Balloon Angioplasty

The earliest approach to treating ISR was BA. Mechanistically, BA compresses and extrudes (axially and longitudinally) intrastent tissue and corrects underlying underexpansion of the stent backbone. One study with IVUS suggested that the lumen enlargement achieved with BA was due (in approximately equal measure) to both additional stent expansion and decrease in neointimal tissue volume.⁹² The technical procedure is relatively straightforward and the complication rate is low. An angioplasty balloon is advanced to the site of the ISR and expanded to nominal pressure. In general, a balloon: vessel ratio of 1.1:1.0 is chosen. The length of the balloon is usually targeted to treat only the restenotic segment of the existing stent rather than the entire stented segment. Failure to achieve full expansion of the angioplasty balloon with standard pressures of 8 to 14 atm can be recognized by a “dog-bone”-like appearance of the balloon. This should promote a switch to noncompliant balloons, which facilitate high-pressure inflation up to approximately 25 atm. Some operators recommend the systematic use of noncompliant

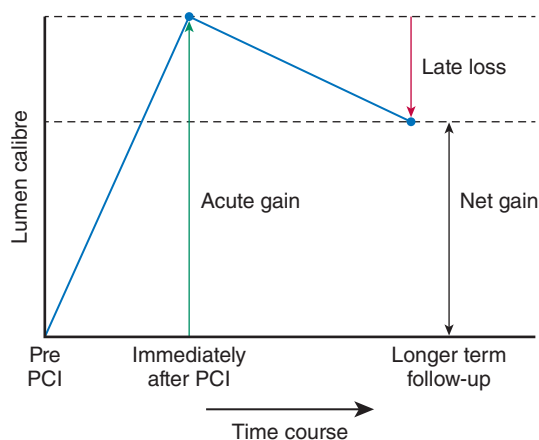


FIGURE 13.6 Acute gain and late luminal loss (LLL) in in-stent restenosis (ISR) percutaneous coronary intervention (PCI). When treating ISR, the aims are to maximize acute gain and minimize LLL.

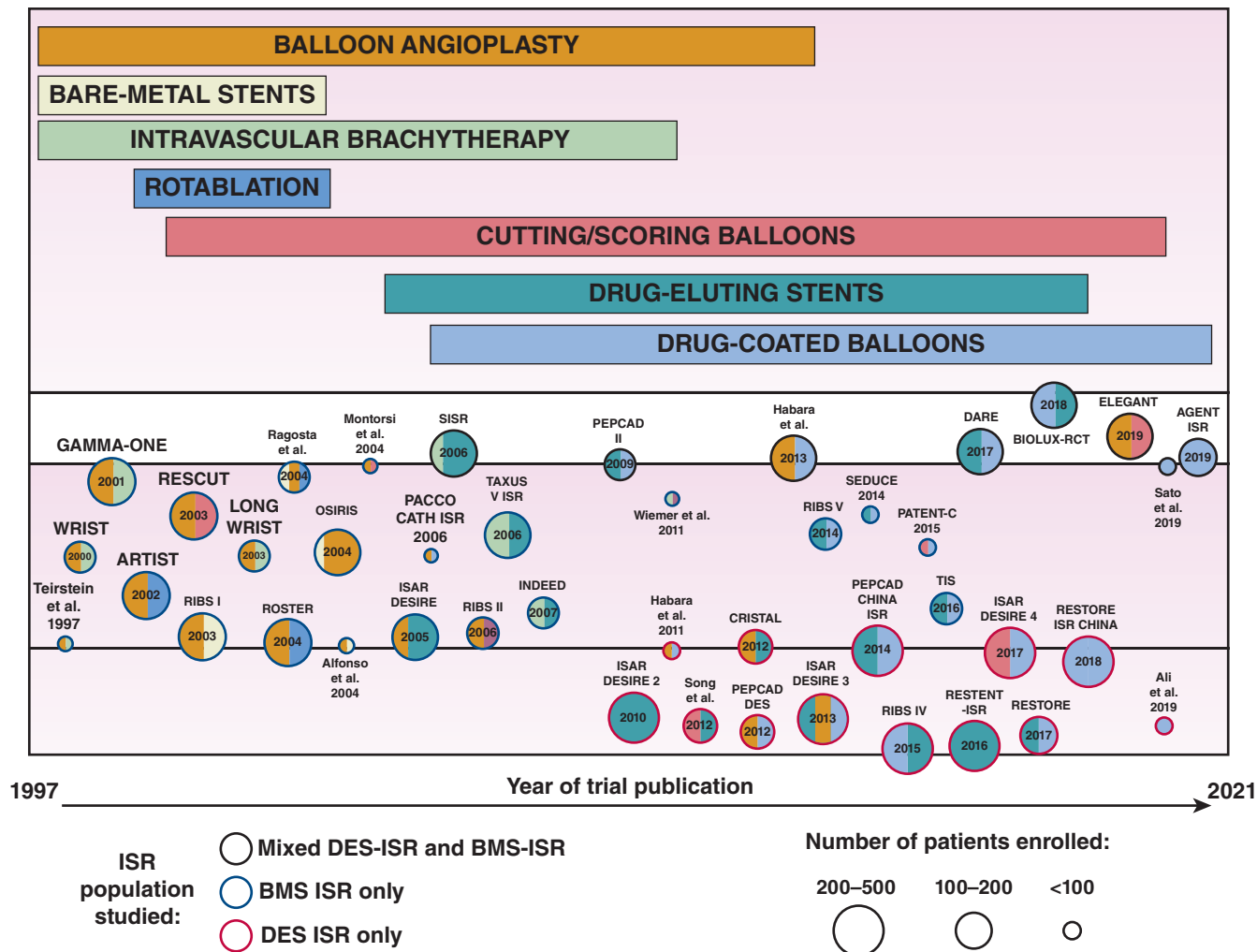


FIGURE 13.7 Trials assessing the treatment of in-stent restenosis (ISR). The sizes of the circles corresponds to the size of the trial. The color of the circles' perimeters indicates the underlying stent type in the ISR population studied. The inner color of the circles indicates the interventional strategies used in the trial, corresponding to the colored bars at the top of the figure. The length of the colored bars at the top of the figure indicates the time span when each therapeutic modality has been studied for the treatment of ISR. Detailed descriptions of the studies and the randomized arms are provided in Table 13.2. Study name abbreviations are provided in the footnotes to Table 13.3. BMS, Bare-metal stent; DES, drug-eluting stent. Adapted from: Alfonso et al.³²

balloons for angioplasty of ISR. Dilation-resistant lesions may be successfully treated with super-high-pressure balloons using inflation pressures of up to 40 to 55 atm, though the increased risk of perforation with this approach should always be considered.⁹³

An important additional technical consideration relevant to BA for ISR is balloon slippage caused by *watermelon seeding*.⁹⁴ This phenomenon occurs when the inflated balloon slips proximally or distally to the intended site of dilatation. This is more commonly encountered in angioplasty for ISR than in de novo disease and may lead to inadvertent trauma to nontarget regions of the treated vessel. This is referred to as "geographic miss" and portends an increased risk of restenosis recurrence. Slow, stepwise inflation of the balloon; sequential angioplasty starting with smaller balloon sizes and working up; the use of a "buddy wire" to stabilize the balloon; and the use of antislip cutting or scoring balloons as an alternative to standard balloons are all strategies which have been used to avoid watermelon seeding.

Although BA alone is still performed in contemporary practice, it is no longer the treatment of choice for ISR. There are several reasons for this. First, residual stenosis after the procedure is relatively high (of the order of $\geq 20\%$). Second, some studies suggest that further early lumen loss occurs in the initial hours after angioplasty. In fact, one study that systematically examined patients both immediately after the intervention and 30 to 60 minutes later reported a significant reduction in MLD during this time window.⁶¹ This was mainly caused by reintrusion of tissue back into the vessel lumen in the minutes and hours after angioplasty. Third, randomized trials have demonstrated the superiority of alternative strategies to BA, including DES implantation and DCB therapy.⁷⁵ In the setting of an under deployed stent, noncompliant or ultra-high-pressure noncompliant balloons may be useful in an attempt to facilitate stent expansion. However, based on current data, isolated BA is not routinely recommended for the treatment of ISR and should be regarded as a lesion preparation method before the use of other therapies.

TABLE 13.2 Randomized Controlled Trials on the Treatment of In-Stent Restenosis: Trial Characteristics^a

REFERENCE OR STUDY	TRIAL CHARACTERISTICS				BASELINE CHARACTERISTICS				
	YEAR	STENT	THERAPY	PATIENTS (n)	AGE (Y)	DM (%)	LENGTH (MM)	RVD (MM)	MLD (MM)
Teirstein et al. ⁵⁰	1997	BMS ^b	IVBT	26	70	27.0	12.9	2.88	1.10
			BA or BMS	29	69	41.0	11.9	2.78	1.03
WRIST ⁵¹	2000	BMS	IVBT	65	63	39.0	28.8	2.71	0.94
			PCI	65	62	45.0	26.7	2.72	0.81
GAMMA-ONE ⁵²	2001	BMS	IVBT	131	58	31.0	19.0	2.69	0.98
			PCI	121	61	31.0	20.3	2.73	0.96
ARTIST ⁵³	2002	BMS	BA	146	61	25.0	13.6	2.65	0.53
			RA	152	62	26.0	13.6	2.63	0.54
RESCUT ⁵⁴	2003	BMS	CB	214	62	24.0		2.58	0.83
			BA	214	61	27.0		2.53	0.84
RIBS I ⁵⁵	2003	BMS	BMS	224	61	27.0	12.7	2.87	0.68
			BA	226	61	26.0	13.0	2.83	0.67
Long WRIST ⁵⁶	2003	BMS	PCI	60	61	37.0	29.1	2.55	0.70
			IVBT	60	63	42.0	29.2	2.57	0.80
OSIRIS ⁵⁷	2004	BMS	BA	102	65	27.5		2.61	
			SIR	99	65	27.3		2.60	
			SIRhd	99	65	32.2		2.57	
Ragosta et al. ⁵⁸	2004	BMS	BA	29	63	21.0	5.1	3.02	0.79
			BMS	29	64	10.0	7.3	3.12	0.85
			RA	30	59	47.0	20.6	2.81	0.69
			BMS	25	59	32.0	18.2	2.99	0.79
Montorsi et al. ⁵⁹	2004	BMS	BA	25	61			3.19	1.07
			CB	25	66			3.28	0.93
ROSTER ⁶⁰	2004	BMS	RA	100	63	31.0	18.6	2.85	0.82
			BA or BMS	100	65	30.0	16.7	2.82	0.92
Alfonso et al. ⁶¹	2005	BMS	BMS	20	66	40.0	12.8	2.55	0.91
			BA	20	66	30.0	12.0	2.55	1.00
ISAR-DESIRE ⁶²	2005	BMS	DES-S	100	63	31.0	12.4	2.60	0.91
			DES-P	100	65	27.0	11.5	2.60	0.97
			BA	100	64	25.0	12.3	2.57	0.95
PACCOATH-ISR ⁶³	2006	BMS	DCB	26	64	15.0	17.9	2.94	0.75
			BA	26	64	15.0	18.1	2.95	0.67
RIBS II ⁶⁴	2006	BMS	DES	76	64	38.0	16.9	2.66	0.74
			BA	74	64	31.0	15.7	2.68	0.70
SISR ⁶⁵	2006	DES-BMS	DES	259	63	33.3	17.2	2.62	0.78
			IVBT	125	64	29.6	16.8	2.64	0.86
TAXUS V ISR ⁶⁶	2006	BMS	IVBT	201	63	30.3	15.0	2.61	0.83
			DES-P	195	63	40.0	15.9	2.68	0.80
INDEED ⁶⁷	2007	BMS	DES	65	61	30.8	27.5	2.77	0.78
			IVBT	64	60	31.3	27.8	2.67	0.81
PEPCAD II ⁶⁸	2009	DES-BMS	DCB	66	65	33.3	15.7	2.85	0.74
			DES	65	65	26.2	15.4	2.83	0.77
ISAR-DESIRE 2 ⁶⁹	2010	DES	DES-P	225	67	38.8	12.5	2.75	0.95
			DES-S	225	66	38.2	12.7	2.78	1.02
Habara et al. ⁷⁰	2011	DES	DCB	25	70	56.0	12.7	2.69	0.99
			BA	25	69	68.0	13.2	2.90	0.92
Wiemer et al. ⁷¹	2011		DES	44	65	49.0	25.2	2.89	0.70
			IVBT	47	64	49.0	17.2	2.77	0.85
PEPCAD-DES ⁷²	2012	DES	DCB	72	70	36.1	11.2	2.29	0.66
			BA	38	64	34.2	12.2	2.30	0.62

Continued

TABLE 13.2 Randomized Controlled Trials on the Treatment of In-Stent Restenosis: Trial Characteristics^a—cont'd

REFERENCE OR STUDY	TRIAL CHARACTERISTICS				BASELINE CHARACTERISTICS				
	YEAR	STENT	THERAPY	PATIENTS (n)	AGE (Y)	DM (%)	LENGTH (MM)	RVD (MM)	MLD (MM)
Song et al. ⁷³	2012	DES	CB	48	62	31.2	7.5	2.93	0.80
			DES-S	48	65	37.5	8.6	3.18	0.68
			S-DES-d	32	61	25.0	22.2	3.19	0.94
			E-DES-d	34	65	35.3	22.5	3.43	0.75
CRISTAL ⁷⁴	2012	DES	DES-S	136	68	39.0	14.6	2.60	1.09
			BA	61	67	38.0	13.4	2.50	1.58
ISAR-DESIRE 3 ⁷⁵	2013	DES	DCB	137	68	41.0		2.75	0.97
			DES-P	131	69	47.0		2.80	0.93
			BA	134	67	37.0		2.72	0.88
Habara et al. ⁷⁶	2013	DES/BMS	DCB	137	68	46.0	12.8	2.52	0.86
			BA	71	70	42.0	13.7	2.49	0.84
RIBS V ⁷⁷	2014	BMS	DCB	95	67	32.0	13.7	2.64	1.02
			DES-E	94	64	20.0	13.8	2.64	0.93
PEPCAD-CHINA ISR ⁷⁸	2014	DES	DCB	109	62	40.0	12.5	2.66	0.85
			DES-P	106	62	33.0	13.8	2.72	0.86
SEDUCE ⁷⁹	2014	BMS	DCB	25	68	24.0		3.00	0.98
			DES-E	25	64	4.0		2.85	0.57
RIBS IV ⁸⁰	2015	DES	DCB	154	66	49	10.4	2.59	0.79
			DES-E	155	66	43	10.7	2.67	0.75
PATENT-C ⁸¹	2015	BMS	Standard SB	28	64	35.7	13.8	2.54	0.73
			Paclitaxel-coated SB	33	65	42.4	16.5	2.72	0.90
TIS ⁸²	2016	BMS	DCB	68	65.6	25.0	22.5	2.64	0.92
			DES-E	68	65.5	26.5	28.5	2.66	0.79
RESTENT-ISR ⁸³	2016	DES	DES-E	158	64.1	36.7	22.5	3.07	0.78
			DES-Z	146	62.2	36.3	24.7	3.15	0.89
ISAR-DESIRE 4 ⁸⁴	2017	DES	SB before DCB	125	69.4	40.8		2.96	1.01
			Standard treatment before DCB	127	69.4	43.3		2.89	0.94
DARE ⁸⁵	2017	DES-BMS	DCB	137	66	42		2.56	0.77
			DES-E	141	65	46		2.59	0.79
RESTORE ⁸⁶	2017	DES	DCB	86	67	50.0	18.1	2.85	0.63
			DES-E	86	66	44.2	17.4	3.06	0.63
BIOLUX-RCT ⁸⁷	2018	DES-BMS	DCB	157	67.2	30.6	5.8	3.0	1.0
			DES	72	69.4	33.3	7.2	2.9	0.9
RESTORE ISR CHINA ⁸⁸	2018	DES	RESTORE DCB	120	63.6	38.3	16.5	2.79	0.91
			SEQUENT PLEASE DCB	120	63.9	38.3	16.2	2.71	0.90
Ali et al. ⁸⁹	2019	DES	PACLITAXEL DCB	25	58.6	76	13.3	2.42	0.80
			SIROLIMUS DCB	25	61.6	72	14.2	2.53	0.81
ELEGANT ⁹⁰	2019	DES-BMS	Nonslip balloon before DCB	105	70.0	51.4	13.8	2.56	0.93
			HPNCB before DCB	105	68.9	47.6	13.3	2.54	0.91
Sato et al. ⁹¹	2019	DES-BMS	ELCA + DCB	20	69.0	50.0	13.9	2.75	0.67
			DCB	20	69.1	75.0	15.5	2.83	1.00
AGENT ISR ⁸⁹	2019	DES-BMS	Agent DCB	65	68	36.9	11.7	2.60	0.75
			SeQuent DCB	60	69	36.7	13.3	2.48	0.65

^aSee footnotes in Table 13.3 for abbreviations.^bOnly 62% bare-metal stent in-stent restenosis.

TABLE 13.3 Randomized Controlled Trials on the Treatment of In-Stent Restenosis: Angiographic and Clinical Endpoints^a

TRIAL CHARACTERISTICS				ANGIOGRAPHIC ENDPOINTS					CLINICAL ENDPOINTS					
REFERENCE OR STUDY	YEAR	THERAPY	TIME (MO)	RE (%)	ISTLL (MM)	ISGLL (MM)	MLD (MM)	DS (%)	TIME (MO)	MACE (%)	DEATH (%)	MI (%)	TLR (%)	TVR (%)
Teirstein et al. ⁵⁰	1997	IVBT	6	17 ^b	0.38 ^b		2.43 ^b	17.0 ^b	12	15.0 ^b	0.0	4.0	12.0 ^b	
		BA/BMS		54	1.03		1.85	37.0		48.0	3.0	0.0	45.0	
WRIST ⁵¹	2000	IVBT	6	22 ^b	0.22 ^b		2.03 ^b	30.0 ^b	12	35.3 ^b	6.2	9.2	23.0 ^b	33.8 ^b
		PCI		60	1.00		1.24	57.0		67.3	6.2	9.2	63.1	67.6
GAMMA-ONE ⁵²	2001	IVBT	6	32 ^b	0.73 ^b		1.78 ^b	46.0 ^b	9	28.2 ^b	3.1	9.9	24.4 ^b	31.3 ^b
		PCI		55	1.14		1.37	53.0		43.8	0.8	4.1	42.1	46.3
ARTIST ⁵³	2002	BA	6	51 ^b	0.67 ^b		1.20 ^b	56.0 ^b	6	20.4			31.0	
		RA		64	0.91		0.99	63.0		9.9 ^b			39.0	
RESCUT ⁵⁴	2003	CB	7	30	0.56		1.61	39.0	7	16.4	1.4	1.4	13.5	
		BA		31	0.62		1.55	40.0		15.4	0.9	1.4	13.1	
RIBS I ⁵⁵	2003	BMS	6	38	1.12	1.06	1.63	45.0	12	23.0	4.0	2.2		19.6
		BA		39	0.73 ^b	0.72	1.52	46.0		29.0	3.0	5.3		24.3
Long WRIST ⁵⁶	2003	PCI	4–8	73	0.99	0.85	0.93	65.0	12	63.3	1.7	18.3	61.7	
		IVBT		45 ^b	0.67 ^b	0.65 ^b	1.23	54.0 ^b		42.2 ^b	6.8	23.7	39.0 ^b	
OSIRIS ⁵⁷	2004	BA	6	42	0.60		1.53	43.7	12	27.5	0.0	1.0		25.5
		SIR		39	0.72		1.37	45.8		29.3	3.0	0.0		24.2
		SIRhd		22 ^b	0.49 ^b		1.66 ^b	38.1		18.2	2.0	0.0		15.2
Ragosta et al. ⁵⁸	2004	BA							9	21.0	0.0	7.2		17.0
		BMS								7.0	3.6	3.6		3.6
		RA								43.0	6.6	3.3		40.0
		BMS								32.0	0.0	4.0		32.0
Montorsi et al. ⁵⁹	2004	BA							6	28.0	0.0		40.0	
		CB								17.0	0.0		12.5 ^b	
ROSTER ⁶⁰	2004	RA	9	42					12	38.0 ^b	2.0	3.0	32.0	
		BA/BMS		56						52.0	2.0	3.0	45.0	
Alfonso et al. ⁶¹	2005	BMS							23	25.0	5.0	0.0		20.0
		BA								50.0	15.0	10.0		35.0
ISAR-DESIRE ⁶²	2005	DES-S	6–8	14 ^b	0.10	0.30	2.12	23.1	12	11.0	2.0	1.0		8.0
		DES-P		22 ^b	0.26	0.55	2.02	26.6		22.0	1.0	2.0		19.0
		BA		45			1.40	45.8		36.0	3.0	0.0		33.0
PACCOATH-ISR ⁶³	2006	DCB	6	5 ^b	0.09 ^b	0.03 ^b	2.31		12	4.0 ^b	4.0	4.0	0.0 ^b	
		BA		43	0.76	0.74	1.60			31.0	0.0	8.0	23.0	
RIBS II ⁶⁴	2006	DES	9	11 ^b		0.13	2.52	8.0	12	11.8 ^b	3.9	2.6		10.5 ^b
		BA		39		0.69	1.54	40.0		31.1	4.1	2.7		29.7

Continued

TABLE 13.3 Randomized Controlled Trials on the Treatment of In-Stent Restenosis: Angiographic and Clinical Endpointsa—cont'd

TRIAL CHARACTERISTICS				ANGIOGRAPHIC ENDPOINTS						CLINICAL ENDPOINTS				
REFERENCE OR STUDY	YEAR	THERAPY	TIME (MO)	RE (%)	ISTLL (MM)	ISGLL (MM)	MLD (MM)	DS (%)	TIME (MO)	MACE (%)	DEATH (%)	MI (%)	TLR (%)	TVR (%)
SISR ⁶⁵	2006	DES	6	20	0.33	0.23	1.80	32.35	9	10.0 ^b	0.0	0.4	8.5 ^b	10.8 ^b
		IVBT		30	0.27	0.33	1.52	40.97		19.2	0.0	0.0	19.2	21.6
TAXUS V ISR ⁶⁶	2006	IVBT	9	31		0.27	1.55	31.2	9	20.1	0.5	4.6	20.1	23.7
		DES-P		15 ^b	0.25	0.11 ^b	1.99	14.5		11.5 ^b	0.0	3.7	7.9 ^b	12.0 ^b
INDEED ⁶⁷	2007	DES	6	6 ^b	0.15 ^b	0.23	2.29	20.42	12	7.7	3.1	1.5	4.6 ^b	
		IVBT		21	0.55	0.40	1.76	32.61		18.8	0.0	0.0	18.8	
PEPCAD II ⁶⁸	2009	DCB	6	4.0	0.19 ^b	0.17 ^b	2.08	29.4	12	7.6	1.5	0.0	6.3	
		DES		12.0	0.45	0.38	2.11	34.2		16.9	0.0	1.5	15.4	
ISAR-DESIRE 2 ⁶⁹	2010	DES-P	6–8	21.0	0.38	0.25	2.16	25.4	12	19.6	4.5	1.8	13.8	
		DES-S		19.0	0.40	0.26	2.14	26.6		20.4	3.4	2.7	14.3	
Habara et al. ⁷⁰	2011	DCB	6	9.0 ^b	0.18 ^b	0.17 ^b	1.82	34.2	6	4.3 ^b	0.0	0.0	4.3 ^b	
		BA		63.0	0.72	0.72	1.28	58.0		41.7	0.0	0.0	41.7	
Wiemer et al. ⁷¹	2011	DES	6	4.0 ^b	0.09 ^b		2.66	7.78	12	4.0	2.0	0.0	2.0	2.0
		IVBT		23.0	0.39		1.75	36.9		27.0	2.0	6.0	16.0	19.0
PEPCAD-DES ⁷²	2012	DCB	6	17.0	0.43	0.32	1.75	29.6	6	16.7 ^b	1.4	0.0	15.3 ^b	
		BA		58.0	1.03	0.99	1.10	51.1		50.0	10.5	2.6	36.8	
Song et al. ⁷³	2012	CB	9	21.0	0.30	0.25	2.08	16.5	12	6.3	0.0	0.0	6.3	6.3
		DES-S		3.0	0.02	0.06 ^b	2.57	12.5		6.3	0.0	6.3	0.0	0.0
		S-DES-d		5.0	0.13	0.13	2.58	25		9.6	3.1	3.1	3.1	3.1
		E-DES-d		14.0	0.07 ^b	0.07	2.71	18		8.8	2.9	2.9	5.8	5.8
CRISTAL ⁷⁴	2012	DES-S	12	11.0	0.37		2.14 ^b	21.0 ^b	12		2.2	2.9	5.9	2.2
		BA		14.0	0.41		1.71	29.8			1.6	1.6	13.1	0.0
ISAR-DESIRE 3 ⁷⁵	2013	DCB	6–8	27.0 ^b	0.37		1.79	38		23.5	2.2	2.1	22.1	24.2
		DES-P		24.0 ^b	0.34		1.82	37.4		19.3	4.6	2.4	13.5	16.6
		BA		57.0	0.70		1.26	54.1		46.2	5.3	1.5	43.5	45.1
Habara et al. ⁷⁶	2013	DCB	6	4.3 ^b	0.11 ^b	0.18 ^b	1.87 ^b	28.1 ^b	6	6.6 ^b	0.0	0.0	2.9 ^b	6.6 ^b
		BA		31.9	0.49	0.72	1.42	44.1		31.0	0.0	0.0	31.0	31.0
RIBS V ⁷⁷	2014	DCB	6	9.5		0.14	2.03	24	12	8.0	4.0	3.0	6.0	6.0
		DES-E		4.7		0.04	2.44 ^b	13 ^b		6.0	0.0	4.0	1.0	2.0
PEPCAD-CHINA ISR ⁷⁸	2014	DCB	9	18.6	0.54	0.46	1.80	29	12	16.5	0.0	3.7	14.7	16.5
		DES-P		23.8	0.62	0.55	1.76	31		16.0	2.0	6.6	10.4	16.0
SEDUCE ⁷⁹	2014	DCB	9	9.1	0.28	0.16	2.13	26.4	12		4.2	0	4.2	8.3
		DES-E		0.0	0.07	0.08	2.54 ^b	11.4 ^b			4	4	8	16.0
RIBS IV ⁸⁰	2015	DCB	9	19		0.30	1.80	30	12	18	1.9	3.0	13.0	16.2
		DES-E		11		0.18	2.03^b	23 ^b		10 ^b	2.6	1.3	4.5 ^b	8.4 ^b
PATENT-C ⁸¹	2015	Standard SB	6	40.7		0.48	1.39	46.8	6	32.1	Cardiac death	TVMI	32.1	—
		Paclitaxel-coated SB		7.4 ^b		0.17^b	1.80 ^b	33.7 ^b		6.1 ^b	Cardiac death	TVMI	3.0 ^b	—

TIS ⁸²	2016	DCB	12	8.7		0.09^b	2.09	26.2	12	10.3	Cardiac death	1.5	—	7.4
		DES-E		19.1 ^b		0.44	2.07	30.9		19.1	Cardiac death	1.5	—	16.2
RESTENT-ISR ⁸³	2016	DES-E	9		0.40		2.54	16.7	36	10.1	0.6	1.9	14.5	
		DES-Z			0.45		2.53	17.4		9.6	2.1	2.7	21.2	
ISAR-DESIRE 4 ⁸⁴	2017	SB before DCB	6–8	18.5 ^b		0.31	1.95	35^b	12	18.4	1.6	3.2	16.2	—
		Standard treatment before DCB		32.0		0.41	1.77 ^b	40.4		23.3	1.7	1.6	21.8	—
DARE ⁸⁵	2017	DCB	6	18.1		0.17 ^b	1.71	36.1	12	10.9	0.7	2.2	—	8.8
		DES-E		20.9		0.45	1.74	33.8		9.2	1.4	2.8	—	7.1
RESTORE ⁸⁶	2017	DCB	9	19.5	0.20	0.15	1.8 ^b	34	12	7.0	0.0	1.2	5.8	5.8
		DES-E		5.6	0.27	0.19	2.09	26		4.7	0.0	3.5	1.2	1.2
BIOLUX-RCT ⁸⁷	2018	DCB	6		0.03	−0.02	2.2.	28.5	18	17.9	Cardiac death	TVMI	—	13.5
		DES			0.20	0.13	2.2	23.7 ^b		18.6	Cardiac death	TVMI	—	11.6
RESTORE ISR CHINA ⁸⁸	2018	RESTORE DCB	9	24.6	0.48	0.39	1.64	38.9	12	13.3	0.0	2.5	13.3	23.3
		SEQUENT PLEASE DCB		18.8	0.42	0.35	1.71	34.5		12.6	0.0	3.4	11.8	12.6 ^b
Ali et al. ⁸⁹	2019	PACLITAXEL DCB	6	—	0.37	0.31	1.99	19.9	12	16	0.0	—	16	—
		SIROLIMUS DCB		—	0.26	0.18	1.99	17.8		12	0.0	—	12	—
ELEGANT ⁹⁰	2019	NON-SLIP BAL-LOON PRE DCB	8	12.9	—	0.28	1.82	30.4	8	7.0	1.0	0.0	6.0	7.0
		HPNCB PRE DCB		15.2	—	0.27	1.71	33.1		9.7	3.9	1.9	7.8	9.7
Sato et al. ⁹¹	2019	ELCA + DCB	12	20	—	−0.25	—	—	12	—	—	—	10.0	—
		DCB		20	—	−0.33	—	—		—	—	—	20.0	—
AGENT ISR ⁸⁹	2019	Agent DCB	6	13.7	0.397		1.62	20.7	12		3.1	4.6	7.7	9.2
		SeQuent DCB		22.4	0.393		1.51	20.2			1.7	3.3	10.0	11.7

^aDetails of the literature search are given in the Supplemental Materials.

^bP < .05.

Agent DCB, AGENT Drug Coated Balloon; AGENT ISR, Comparison of Agent™ and SeQuent® Please Paclitaxel Coated Balloon Catheters in Coronary In-stent Restenosis; ARTIST, Angioplasty Versus Rotational Atherectomy for Treatment of Diffuse In-Stent Restenosis Trial; BA, balloon angioplasty; BIOLUX, Clinical Performance of the Pantera LUX Paclitaxel Releasing Balloon Versus the Drug Eluting Orsiro Hybrid Stent System in Patients With In-stent Restenosis; CB, cutting balloon; CRISTAL, A Prospective, Randomized, Multi-Center Comparison of the CYPHER Select™ Sirolimus-Eluting Stent and Balloon Re-Angioplasty for Treatment of Patients With Intra-Des Restenosis; DARE, Drug Eluting bAlloon for In-stent REstenosis. Multi-center, Randomized Trial to Study the Effect of the SeQuent Please Drug-eluting Balloon Versus the Xience Prime Drug-eluting Stent for the Treatment of In-stent Restenosis; DCB, drug-coated balloon; DES, drug-eluting stent(s); DES-E, everolimus drug eluting stent(s); DES-P, paclitaxel drug-eluting stent(s); DES-S, sirolimus drug-eluting stent(s); DES-Z, zotarolimus drug eluting stent; DM, diabetes mellitus; E-DES-d, everolimus-eluting stent for diffuse restenosis; ELEGANT, Effect of Combination of Non-slip Element Balloon (NSE) and drug-coated balloon (DCB) for In-stent Restenosis Lesions; GAMMA-ONE, Localized Intracoronary Gamma-Radiation Therapy to Inhibit the Recurrence of Restenosis after Stenting; HPNCB PRE DCB, High pressure non compliant balloon angioplasty pre drug coated balloon; INDEED, Treatment of diffuse In-stent restenosis with Drug-Eluting stents vs. intracoronary beta-radiation therapy; ISAR-DESIRE, Intracoronary Stenting or Angioplasty for Restenosis Reduction, Drug-Eluting Stents for In-Stent Restenosis; ISAR-DESIRE, Intracoronary Stenting and Angiographic Results, Drug Eluting Stents for In-Stent Restenosis 2; ISGLL, in-segment late loss; ISTLL, in-stent late loss; IVBT, intravascular brachytherapy; LL, lesion length; Long WRIST, Washington Radiation for In-Stent Restenosis Trial for Long Lesions; MACE, major adverse cardiac events (including death or cardiac death, myocardial infarction [MI], and target lesion revascularization [TLR] or target vessel revascularization [TVR] as considered in each trial for the combined outcome measure); MLD, minimal lumen diameter; OSIRIS, Oral Sirolimus to Inhibit Recurrent In-stent Stenosis; PACCOATH-ISR, Treatment of in-stent Restenosis by Paclitaxel Coated PTCA Balloons; PATENT-C, Treatment of Coronary In-stent Restenosis by a Paclitaxel Coated AngioSculpt Scoring Balloon; PCI, percutaneous coronary intervention (BA, rotational atherectomy [RA], excimer coronary laser atherectomy [ECLA], BMS); PEPCAD, The Paclitaxel-Eluting PTCA-Balloon Catheter to Treat Small Vessel Coronary Artery Disease. A Pilot Study; PEPCAD II, The Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease to Treat In-Stent Restenosis, A Comparison to the Paclitaxel-Eluting Taxus™ Stent. A Pilot Study; PEPCAD-CHINA, A Multicenter, Randomized, Active Controlled Clinical Study to Evaluate the Safety and Efficacy of the Treatment of In-stent Restenosis Lesion by Paclitaxel-eluting PTCA-Balloon Catheter Versus Paclitaxel-eluting Stent; PEPCAD DES, Treatment of DES-In-Stent Restenosis With SeQuent® Please Paclitaxel Eluting PTCA Catheter; RE, binary restenosis; RA, rotational atherectomy; RESCUT, Restenosis Cutting Balloon Evaluation Trial; RESTENT ISR, Prospective, Single-blinded, Randomized Comparison of the Clinical and Angiographic Results With Intravascular Analysis of Everolimus-Eluting Versus Zotarolimus-Eluting stents for In-Stent Restenosis (ISR) Lesions, Volumetric Analysis With Intravascular Ultrasound (IVUS), Phase IV Multicenter Trial; RESTORE, Treatment of Drug-Eluting Stent Restenosis Using Drug-Eluting Stents vs. Drug-Coated Balloon for Preventing Recurrent In-Stent Restenosis; RESTORE CHINA, Compare the Efficacy and Safety of RESTORE DEB and SeQuent Please in Chinese Patient With Coronary In-stent Restenosis; RESTORE ISR CHINA, Compare the Efficacy and Safety of RESTORE DEB and SeQuent® Please in Chinese Patient With Coronary In-stent Restenosis; RIBS I, Restenosis Intra-stent Balloon Angioplasty Versus Elective Stenting; RIBS II, Restenosis Intra-stent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting; RIBS V, Restenosis Intra-stent: Drug-eluting Balloon vs. Everolimus-eluting Stent; ROSTER, Randomized Trial of Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-Stent Restenosis; RVD, reference vessel diameter; S-DES-d, sirolimus-eluting stent for diffuse restenosis; SEDUCE, Safety and Efficacy of a Drug eluting balloon in Coronary artery restenosis; SeQuent DCB, SeQuent drug coated balloon; SEQUENT PLEASE DCB, SeQuent Please drug coated balloon; SIR, usual dose oral sirolimus; SIRhd, high-dose oral sirolimus; SISIR, Sirolimus-Eluting Stent vs. Brachytherapy in Patients With Bare Metal In-Stent Restenosis; TAXUS V ISR, A Prospective, Randomized Trial Evaluating Slow-Release Formulation TAXUS Paclitaxel-Eluting Coronary Stent in the Treatment of In-Stent Restenosis; TIS, Treatment of Coronary In-Stent Restenosis; WRIST, Washington Radiation for In-Stent restenosis Trial.





Bare-Metal Stenting

Bare-metal stent implantation was also assessed as an approach for the treatment of BMS ISR and demonstrated some benefits compared with BA with regard to acute luminal gain.⁹⁵ Whereas the RIBS (Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting) I trial reported comparable results overall with BMS and BA, subanalysis of this trial reported that BMS were superior to BA in large vessels (>3-mm reference vessel diameter) and in “edge-ISR.”⁵⁵ However, there are no trials assessing the value of BMS implantation for the treatment of DES ISR, and the role of stenting with BMS in the management of ISR is largely of historical interest.

Intravascular Brachytherapy

Intracoronary radiation therapy—commonly known as intravascular brachytherapy (IVBT)—has also been successfully used to treat patients with ISR. The therapy is delivered at the time of mechanical treatment of the stenosed stent and is termed brachytherapy because of the short distance from the radiation source to the target tissue. The aim of this treatment modality is to impede new intimal cell growth within the target area without damage to the surrounding tissue. The radiation achieves this effect via two primary methods: direct damage secondary to ionizing emissions, and injury secondary to free radical generation.⁹⁶ The anti-inflammatory effects of the radiation may also be useful in the setting of ISR. Radioactive material (typically in the form of seeds) is delivered to the target lesion inside a specialized catheter, which is left to dwell in the coronary artery for a period of between 2 to 3 and 30 to 45 minutes, depending on the type of radiation source. Both beta and gamma radiation sources have been successfully used to treat ISR. Gamma radiation sources have high energy (~0.2–10 MeV), high tissue penetration, and longer dwell times and therefore require more stringent radiation protection protocols. Beta radiation has lower energy, lesser penetration, shorter dwell times, and a reduced requirement for radiation shielding. Preclinical investigation with both sources has demonstrated effective inhibition of neointimal hyperplasia in porcine models of coronary intervention.^{97,98}

Initial double-blinded randomized trials showed improvement in both angiographic and clinical outcomes at 6 to 12 months of follow-up with both gamma and beta radiation sources in comparison with standard BA.^{50,52,98-100} There are two main limitations of IVBT, the requirement for specialized laboratory equipment with unwieldy treatment protocols and evidence of systematic impaired arterial healing after intervention. This latter issue foreshadowed many of the problems that would be subsequently observed with DES technology and was associated with a spectrum of adverse events, including geographic miss, edge restenosis, late stent thrombosis, and late *catch-up* restenosis.^{16,102,103}

Drug-eluting stents were found to be superior to IVBT in the setting of BMS ISR.⁶⁴⁻⁶⁶ There are no randomized data on the use of IVBT in the setting of DES ISR. Nonrandomized data have suggested that IVBT could have a niche role in the management of recurrent ISR.^{104,105} Overall, this lack of evidence, in conjunction with the inferior results in

comparison to DES in available RCTs, has prevented the common use of this technology in current practice. It may still have a role in the treatment of patients with recurrent or recalcitrant ISR after the failure of conventional, first-line therapies, but this should be reserved for specialist centers with experience with this technology.

Rotational Atherectomy

Rotational atherectomy (RA) is an ablative technique performed using a metal burr studded with diamonds, which is advanced to the site of the restenosis and rotated at high speeds (in the order of 150,000–200,000 rpm). By pulverizing stenotic plaque to microparticles of 20- to 50- μ m diameter (small enough to pass through the coronary microcirculation), additional lumen enlargement can be achieved during PCI. This technique may also be useful for lesion preparation in the setting of underexpanded stents secondary to calcification. While there are randomized data comparing RA with BA in BMS ISR,^{53,60} there are no randomized trials assessing RA in DES ISR. Despite this lack of evidence in the DES era, RA is occasionally used as an adjunctive technique for ISR in specific clinical settings, for example, lesion modification in the setting of ISR caused by heavily calcified in-stent plaques, or even to treat stent underexpansion not amenable to treatment by other techniques.¹⁰⁵⁻¹⁰⁷ RA-PCI for ISR carries some specific risks (i.e., burr entrapment within the ISR lesion, vessel perforation). RA is rarely required in the modern management of ISR given that newer and safer strategies are available to tackle ISR in the setting of severe calcification.

CUTTING AND SCORING BALLOONS

Cutting balloons are composed of standard balloon catheters mounted with lateral metallic blades known as atherotomes (with a working height of ~127 μ m), which, on inflation of the balloon, incise into the treated stenotic plaque (Figure 13.8). There are two main advantages to their use:

- The incision of the blades into the stenotic plaque may favor tissue extrusion.
- The interaction of the blades with the plaque serves to anchor the balloon in the plaque, preventing watermelon seeding; this in turn might reduce problems related to geographic miss.⁹⁴

Scoring balloons have a broadly similar mechanistic basis. The main difference is that instead of lateral metallic blades, low-profile nitinol wires (of the order of 125 μ m) are mounted on the surface of the balloon catheter in a spiral formation (see Figure 13.8). As a result, the deliverability and flexibility of the catheters are increased, albeit at the expense of a lesser degree of plaque incision. However, anchoring of the balloon at the target lesion is maintained. The use of a scoring balloon before angioplasty with DCBs has been shown to improve the antirestenotic efficacy of DCB angioplasty, possibly by facilitating better drug diffusion through more extensively disrupted intrastent tissue.⁸⁴ A nonslip balloon has shown similar efficacy to high pressure noncompliant balloons in lesion preparation before DCB treatment for ISR.⁹⁰

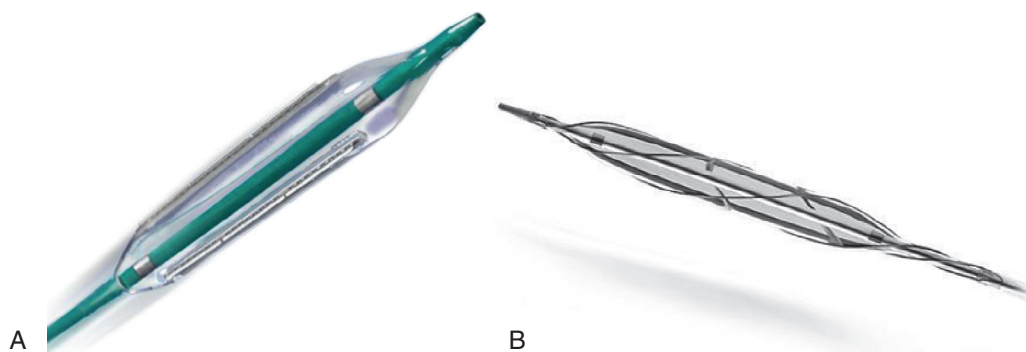


FIGURE 13.8 Cutting and scoring balloon structure. **A**, Flextome cutting balloon device. The device consists of a balloon catheter mounted with lateral metallic blades known as atherotomes. **B**, AngioSculpt scoring balloon device. The device is composed of a semicompliant angioplasty balloon mounted with low-profile nitinol wires in spiral formation. (**A**, Image downloaded from www.bostonscientific.com. **B**, Reused with permission from AngioScore.)

Both cutting and scoring roles may play a valuable role in lesion preparation before DES or DCB in the treatment of patients with ISR.¹⁰⁹ However, as a stand-alone treatment they suffer from similar limitations to BA and are hindered by their inability to inhibit neointimal proliferation.^{54,110}

Adjunctive Medical Therapy

It has been hypothesized that antiinflammatory or antiproliferative medical therapy could reduce the risk of ISR recurrence. In the largest randomized trial of this approach, the OSIRIS (Oral Sirolimus to Inhibit Recurrent In-stent Stenosis) trial, oral sirolimus resulted in a significant improvement in 6-month angiographic parameters.⁵⁷ However, this early benefit was attenuated at longer follow-up and concern regarding potential side effects led to reduced interest in this therapeutic approach.¹¹¹ Currently, there is no clear evidence supporting the use of adjunctive systemic antiproliferative medical treatments in patients with ISR.

Drug-Eluting Stent Implantation

Drug-eluting stents are noted for their ability to inhibit neointimal tissue proliferation^{3,4} and superseded BMS for the treatment of de novo CAD based in part on their associated reduction in restenosis rates.^{3,4} Therefore, their use in the treatment of patients with ISR was logical and is supported by clinical data, with several meta-analyses reporting that DES implantation is the most efficacious treatment for ISR, at least over the short to medium term.^{48,49} RCTs have demonstrated the superiority of DES implantation to BA,^{62,64,74} IVBT,⁶⁴⁻⁶⁶ and paclitaxel DCBs¹¹² for the treatment of ISR. The main downside of the use of DES implantation to treat ISR is that this results in an additional layer of stent metal, which is sometimes referred to as the *onion skin* phenomenon based on the appearance of the multiple stent layers on IVI (Figure 13.9). Indeed, the presence of multiple stent layers can make subsequent treatment of ISR challenging in the event of further recurrence. Therefore, it is essential to ensure that the originally restenosed stent is adequately expanded before implantation of another stent layer. An example of an ISR lesion treated with DES is shown in Figure 13.10.

DES Strategy: Hetero-DES versus Homo-DES

When treating DES ISR with a DES, the operator can choose to use a DES with the same antiproliferative agent (referred to as a *homo-DES strategy*) or a different antiproliferative agent (a *hetero-DES strategy*). The use of a new DES with a different antiproliferative agent is based on the concept that some degree of drug resistance may have contributed to the development of the initial DES ISR. The ISAR-DESIRE (Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-stent REstenosis) 2 trial was the only RCT specifically addressing this issue and reported comparable outcomes with the hetero-DES and homo-DES strategies for sirolimus-eluting stent ISR.⁶⁹ The RIBS-III study reported that a hetero-DES strategy might be beneficial, although it is important to consider that this study was not randomized, with the decisions regarding use of a hetero-DES or homo-DES strategy made by the treating physicians.¹¹³ Although a meta-analysis has also reported potential advantages with the hetero DES strategy, the inclusion of observational data limits interpretation of the findings.¹¹⁴ Because paclitaxel DES are no longer commercially available, this issue may be of limited relevance for clinical practice.

Drug-Coated Balloons

Stent-based interventional modalities, in particular DES implantation, tend to have superior antirestenotic efficacy compared with BA because of the combination of higher acute gain and lower late loss. However, angioplasty with DCBs has emerged as an attractive therapeutic option for ISR, particularly in clinical situations where implantation of another stent layer might be undesirable.

Drug-coated balloon catheters are comprised of standard angioplasty balloons with a matrix coating that is applied to the surface of the balloon (Figure 13.11). The balloon coating is typically composed of two elements: a lipophilic active drug and a spacer or excipient (which increases the solubility of the active drug and facilitates its transfer from the balloon surface to the vessel wall). Preclinical studies have documented effective drug transfer, with evidence of local fibrin deposition as a signature of therapeutic efficacy.¹¹⁵

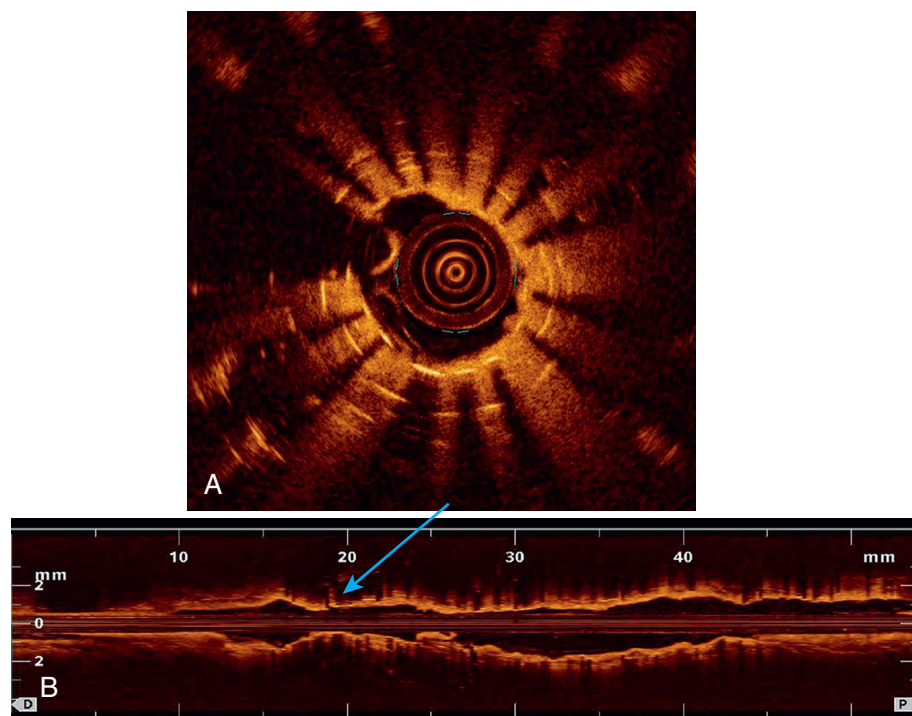


FIGURE 13.9 The cross-sectional view (**A**) shows evidence of multiple layers of metallic stents, referred to as the 'onion skin' phenomenon', with focal severe stent under expansion in the longitudinal view (**B**).

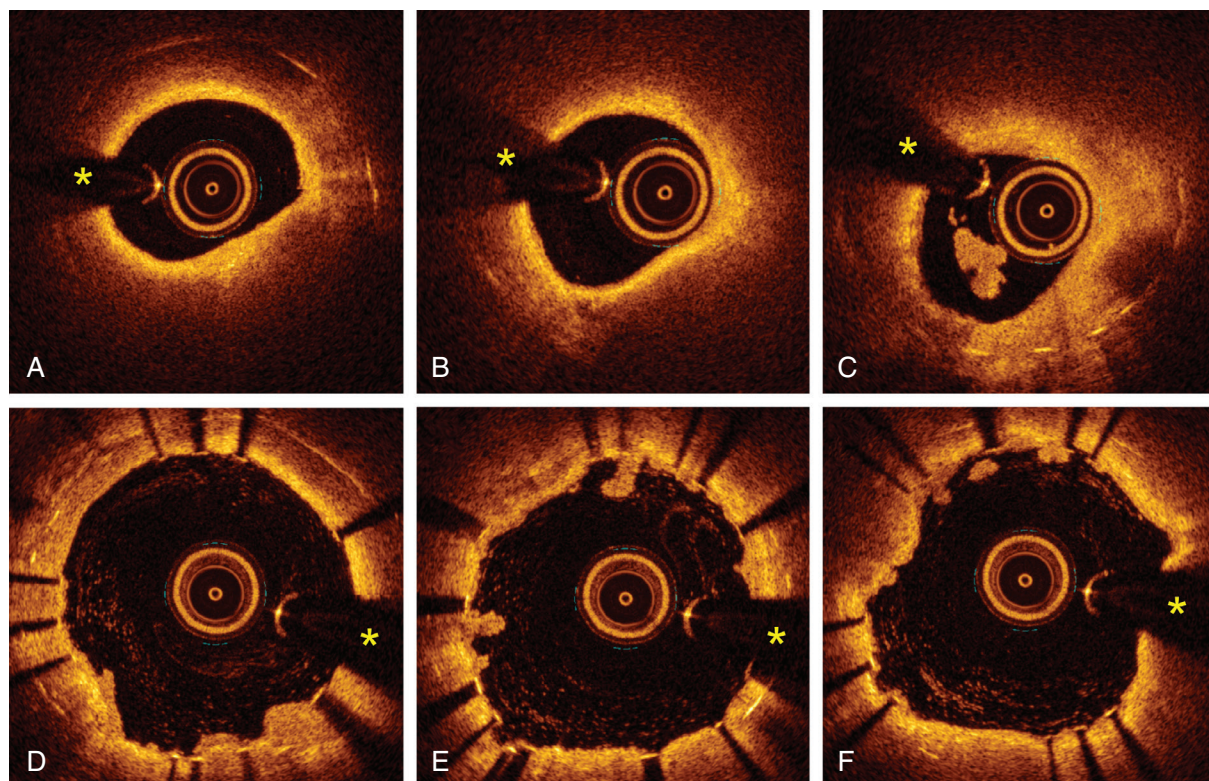


FIGURE 13.10 An 81-year-old man presented with a non-ST-segment elevation myocardial infarction. He had been previously treated with a drug-eluting stent (DES) in the proximal left anterior descending coronary artery 12 years earlier. **A–C**, Optical coherence tomography (OCT) images showing in-stent restenosis as the result of neoatherosclerosis. **A**, A large lipid plaque is visualized, obscuring most of the stent struts that are only visible from the 11 to 3 o'clock positions. Notice also the very bright intimal surface. **B**, The lipid material obstructing the stent virtually shadows all the stent struts. **C**, Neoatherosclerosis associated with a small intraluminal thrombus (stent struts are only visualized from the 3 to 7 o'clock positions). Predilation with a conventional balloon provided a suboptimal angiographic result. **D–F**, OCT findings after repeat DES implantation. A large lumen is obtained, and a double metal layer is visualized. Interestingly, significant protrusion of soft tissue into the lumen can be also recognized. Asterisk denotes wire artifact.

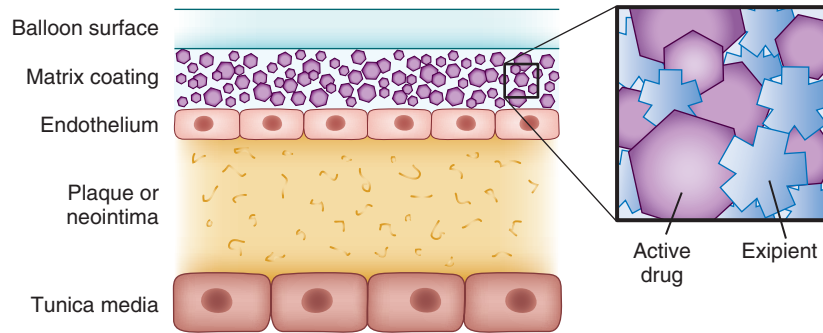


FIGURE 13.11 Drug-coated balloon structure. Drug release is facilitated by a coating that consists of a mixture of lipophilic drug and a hydrophilic spacer or excipient that facilitates faster uptake into the vessel wall. The spacer or excipient combines with the active drug to form a matrix coating that remains on the surface of the balloon catheter.

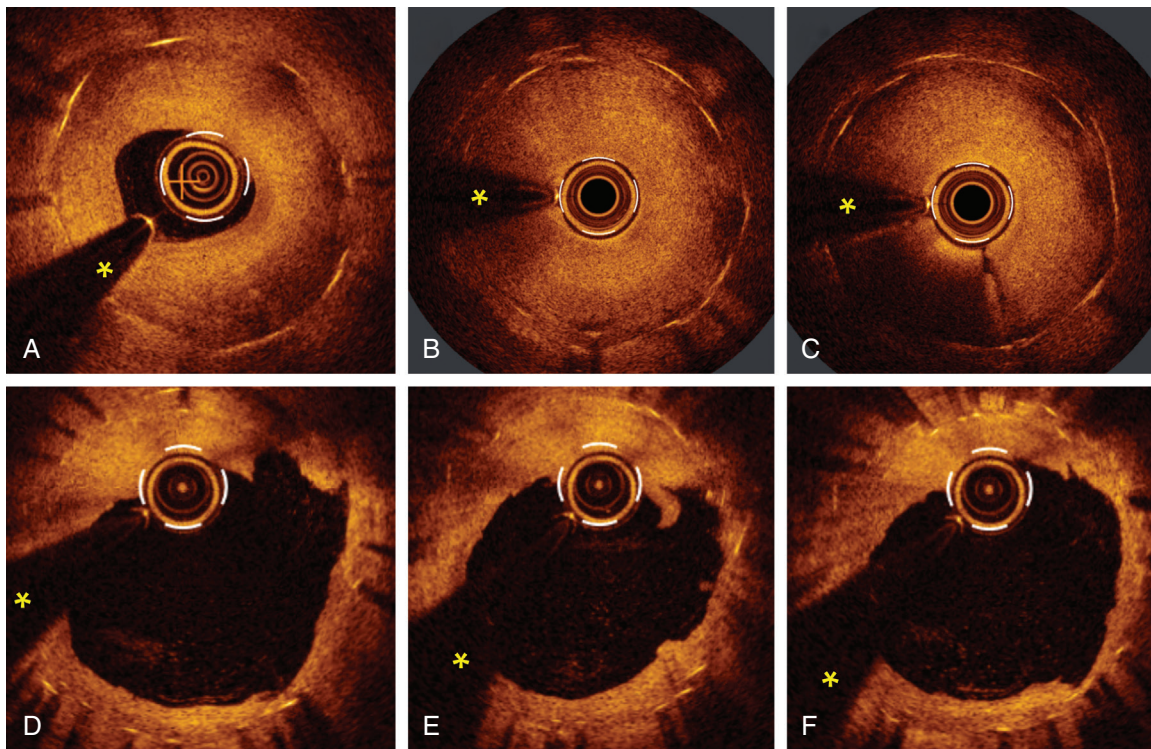


FIGURE 13.12 **A–C**, Optical coherence tomography (OCT) images in a patient presenting with progressive angina and severe (occlusive) in-stent restenosis (ISR) after repeat drug-eluting stent (DES) implantation in the left anterior descending coronary artery. The tissue completely obstructing the stent was largely homogeneous, with a uniform bright pattern consistent with severe neointimal hyperplasia. A double metal layer may be also visualized (**B** and **C**). Some darker tissue is also visualized in confined areas (**C**, from the 6 to 9 o'clock positions). **D–F**, OCT images after the intervention. After conventional noncompliant high-pressure balloon dilation followed by scoring balloon dilation, a drug-coated balloon dilation (DCB) was used, with a satisfactory final result. Notice the large lumen and the residual neointima with some mild dissections. Asterisk denotes wire artifact.

During DCB angioplasty for ISR, the lesion must first be dilated with a standard or noncompliant balloon to extrude and compress the neointima and to correct stent underexpansion, if present. Only after achieving satisfactory initial results should DCB angioplasty be performed, typically with a single 30- to 60-second balloon inflation. Transfer of the antiproliferative drug to the vessel wall results in effective suppression of neointimal hyperplasia.

Drug-coated balloon technology is attractive for the management of ISR because it has the ability to suppress tissue proliferation without requiring the implantation of an additional stent layer. Therefore, in certain situations (i.e., in ISR lesions that already have multiple previous stent layers or ISR lesions in the presence of a major side branch), DCBs may be particularly useful. Another

consideration from a practical perspective is that patients who undergo DCB therapy may require a shorter duration of dual antiplatelet therapy (DAPT) compared with patients after DES implantation. Therefore, if patients are considered to be at high bleeding risk, DCB may represent a practical approach to provide antiproliferative therapy while minimizing the duration of DAPT, and therefore the bleeding risk. Immediate postprocedural results with DCB angioplasty are often inferior to those seen after repeat stenting, but in general, this should not prompt the operator to switch strategy to repeat stenting. OCT images of a patient with ISR treated with DCB therapy are shown in [Figure 13.12](#). Studies of a systematic combined approach using angioplasty with DCB and repeat stenting with DES are lacking.

Paclitaxel Drug-Coated Balloons

The majority of clinical data for DCBs is with paclitaxel-coated DCBs.^{70,88,116} DCBs have been shown in RCTs to be superior to some alternative therapeutic approaches for ISR, including BA.^{72,75,76,117} Although a class effect cannot be assumed, earlier generation PCB devices with reduced efficacy are no longer in widespread clinical use. Moreover, clinical trials have reported broadly comparable outcomes with the most frequently used devices on the market, which combine paclitaxel with iopromide or citrate-based excipients coated DCBs.^{116,118,119} The use of paclitaxel DCBs in the treatment of CAD has been shown in a large meta-analysis to be safe, without any excesses in mortality rate.¹²⁰

Sirolimus Drug-Coated Balloons

In recent years, sirolimus DCBs have been developed, and initial registry data have demonstrated encouraging results in both de novo CAD and ISR.^{121,122} A small RCT reported comparable outcomes with a novel sirolimus DCB balloon in comparison with a paclitaxel DCB.⁸⁹ Of note, there are no trials reporting on the comparison of sirolimus DCB and DES in the management of ISR, and this represents a gap in scientific knowledge. Larger studies may be useful to determine the relative efficacy of sirolimus DCB compared with both paclitaxel DCB and DES. Novel limus-eluting DCBs are also currently under clinical investigation.

Drug-Coated Balloons: The Importance of Lesion Preparation

As a general principle when treating patients with ISR, care must be taken to prepare the ISR lesion adequately. This tenet may be particularly true for ISR lesions when subsequent treatment with a DCB is planned. DCB efficacy is reliant on not only the initial transfer of the antiproliferative drug to the restenotic tissue, but also on retention of the antiproliferative drug. This led to the concept that modifying the restenotic tissue with cutting or scoring balloons before DCB therapy might optimize the delivery and retention of the antiproliferative drug in the restenotic tissue, leading to increased efficacy. The treatment effect of systematic lesion preparation with a scoring balloon was assessed in the ISAR-DESIRE 4 trial, which reported that this approach resulted in increased DCB antirestenotic efficacy.⁸⁴ Both technologies (scoring balloons and DCBs) have recently been combined in one device. This device was slightly more difficult to deliver but showed generally favorable results compared with an uncoated scoring balloon alone in a small study.⁸¹ In current practice, the use of a scoring or cutting balloon followed by angioplasty with DCB using a different balloon catheter likely represents the most useful approach.

Drug-Eluting Stents versus Drug-Coated Balloons for the Treatment of In-Stent Restenosis: Direct Evidence

There are a large number of clinical trials directly comparing the efficacy and safety of DES and paclitaxel DCBs for

ISR.^{77,78,80,82,84-86,122-125} An individual patient data meta-analysis of all available RCTs comparing DES and paclitaxel DCB angioplasty for the treatment of ISR has reported that repeat DES implantation is moderately more effective in reducing the rate of target lesion revascularization (TLR) at 3 years.¹¹² However, this marginal gain in efficacy associated with DES compared with DCB therapy must be balanced against the potential disadvantages associated with implantation of an additional stent layer.

The relative efficacy of DES vs paclitaxel DCB therapy for ISR might also vary depending on whether the restenosed stent is a DES or a BMS.^{127,128} In BMS ISR, outcomes are comparable with DES and DCB. Therefore, given that DCB therapy does not result in an additional stent layer, it could be considered more attractive than DES implantation for the initial treatment of BMS ISR. However, the same analysis reported that for DES ISR, treatment with DES implantation is moderately more effective than DCB therapy regarding the need for TLR.¹²⁸ Importantly, the treatment of DES ISR is associated with inferior late angiographic and clinical outcomes compared with the treatment of BMS ISR, highlighting that DES ISR is generally more challenging to treat.¹²⁹

Bioresorbable Scaffolds

Bioresorbable scaffolds (BRs) have also been studied as a potential therapeutic approach for the treatment of ISR. However, they were associated with a higher subsequent need for TLR compared with the results obtained with DESs in previous studies.¹³⁰ Subsequently, the potential value of systematic predilation with scoring balloon before polymeric BRS implantation in patients with ISR could not be confirmed in the prospective RIBS VI scoring registry.¹³¹ Given that polymeric BRs are no longer commercially available, they have no role in the treatment of ISR in modern practice.¹³² Magnesium-based BRs have been investigated for the treatment of ISR,^{133,134} but currently, there is insufficient evidence to suggest that these devices have any role to play in the treatment of patients with ISR. Treatment of BRS restenosis appears to have similar results to those seen in the treatment of ISR of metallic stents.¹³⁵

Excimer Coronary Laser Atherectomy

Excimer coronary laser atherectomy (ECLA) is a debulking technique that, like RA, can ablate tissue. However, it does this by using ultraviolet spectrum wavelengths to generate heat and shockwaves.^{136,137} Although this therapeutic modality has been shown to be safe,¹³⁸ there is a lack of randomized data assessing ECLA for the treatment of DES ISR. ECLA may still have an adjunctive role in the treatment of ISR,⁹¹ particularly for recurrent or “undilatable” ISR in the setting of severe calcification and an underexpanded stent. In this setting, ECLA may allow for stent expansion, although it might be best viewed as a “bailout strategy” when other techniques have failed. Contrast can be injected during ECLA therapy to induce further barotrauma and microcavitations, although such an approach may be associated with a higher risk of adverse safety events.

Intravascular Lithotripsy

Intravascular lithotripsy (IVL) is an interventional technology that uses localized pulsatile sound waves to modify circumferential vascular calcium.¹³⁹ Although the majority of clinical evidence supporting the use of IVL has been in de novo CAD,¹⁴⁰ there have also been reports of this technique facilitating stent expansion in ISR, albeit as an off-label use.¹⁴⁰⁻¹⁴³ IVL has been used effectively after the failure of conventional therapeutic approaches in patients with “undilatable” ISR.¹⁴⁵ The pulsatile sound waves induce fractures in the calcified plaque, increasing plaque compliance and allowing for increased stent expansion. Additional advantages of IVL over techniques such as RA in the treatment of patients with ISR include that IVL is less dependent on operator experience and appears to be safer.

Coronary Artery Bypass Grafting

Although the management of ISR remains challenging, it is often focal in nature and lends itself to repeat percutaneous intervention, at least in the first instance.⁸ The optimal management strategy for recurrent restenosis remains unclear, though some reports support the feasibility and safety of repeated percutaneous intervention.¹⁴⁶ Bypass surgery undoubtedly plays an important role in

selected patients, particularly if multiple vessels are involved.¹⁴⁷ Systematic evaluation of the role of bypass surgery for ISR is lacking, and there have been no RCTs comparing coronary artery bypass grafting (CABG) with other treatment modalities for ISR. However, an observational analysis has reported that patients treated with CABG for ISR had superior outcomes compared with PCI.¹⁴⁸ Specific ISR clinical scenarios for which CABG should be considered include ISR of the left main stem or ostial LAD,¹⁴⁹ recalcitrant ISR in a major vessel, or ISR with associated multivessel disease.

TREATMENT ALGORITHM

Based on the evidence discussed in this chapter, we present a proposed ISR treatment algorithm (Figure 13.13). This algorithm is intended for the treatment of ISR within the stent, rather than edge restenosis, for which repeat stenting is required in the majority of cases.

Two important factors to consider when managing ISR are the type of ISR (BMS ISR or DES ISR) and mechanical issues preventing adequate stent expansion. This is because the choice of whether to treat ISR with a DES or DCB may be guided by whether it is BMS ISR or DES ISR, and several studies have indicated that the risk of ISR recurrence may

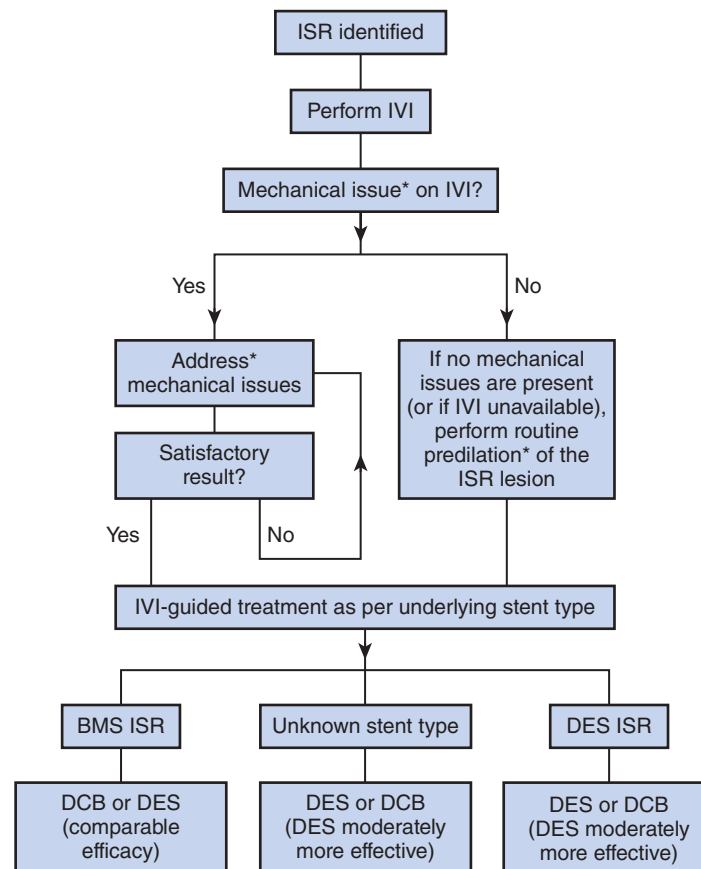


FIGURE 13.13 Algorithm for the management of in-stent restenosis. Asterisk: Mechanical issues can include stent undersizing, stent underexpansion, vessel calcification, stent fracture, and geographic miss. Mechanical issues can be addressed via a variety of methods dependent on the identified pathology and local skill set. These methods can include balloon atherectomy (BA), including a noncompliant or ultra-high-pressure noncompliant balloon, rotational atherectomy, excimer coronary laser atherectomy, intravascular lithotripsy, and cutting and scoring balloons. Predilatation can be performed with BA or cutting or scoring balloons. Cutting and scoring balloons may be particularly useful before planned drug-coated balloon (DCB) therapy. BMS, Bare-metal stent; DES, drug-eluting stent; ISR, in-stent restenosis; IVI, intravascular imaging.



be increased if mechanical issues are not identified and addressed during the ISR PCI procedure.^{30,128}

We recommend the use of IVI to guide the management of all ISR cases when possible. This can be used to identify mechanical issues and define the ISR tissue type and may be useful to inform the interventional strategy. Enhanced fluoroscopic imaging techniques (e.g., StentBoost) can also be helpful and can be used quickly to detect inadequate stent expansion or stent fracture.¹⁵⁰

The interventional strategy can also be guided by the IVI findings. In addition to providing actionable information on sizing of devices, this may also inform the choice of modality for lesion preparation. As mentioned earlier in this chapter, achieving adequate stent expansion is of particular importance in ISR PCI to reduce the risk of further recurrences.

If there are concerns that adequate stent expansion has not been achieved after lesion preparation, then IVI can be repeated. This may inform the subsequent treatment strategy or to determine if additional therapeutic modalities are required to achieve stent expansion. Noncompliant and ultra-high-pressure NC balloons can be used as required, and if the operator intends to subsequently treat the ISR lesion with a DCB, then consideration should be given to the use of cutting or scoring balloons to optimize the delivery and retention of the antiproliferative drug.

After the ISR lesion has been adequately prepared, the next step is deciding on the definitive treatment modality, usually either angioplasty with DCB or repeat stenting with DES. As highlighted in the earlier review of the scientific evidence, both DCB and DES are the most effective therapeutic modalities for the treatment of ISR in the majority of cases, so the initial treatment of ISR should generally consist of one of these two options.

Treatment decisions may also be impacted by intraprocedural findings. For example, after balloon predilation, suboptimal angiographic results may be achieved. This can include significant dissections or persistent residual stenosis. Depending on the extent of these issues, the operator may prefer repeat stenting with DES.

For DES ISR, meta-analysis has shown that repeat DES implantation is moderately more effective than DCB therapy. However, operators need to balance this moderate efficacy benefit against the requirement for implantation of another stent layer. In many cases, initial treatment with a DCB could be preferable. For BMS ISR, outcomes are comparable with DES and DCB. Therefore, the use of a DCB may be preferable in the first instance as it does not result in an additional stent layer.

However, many other factors can impact on clinical decision making when deciding if DES or DCB is the best treatment for ISR (i.e., presence of a significant side branch), and this requires clinical judgment on a case-by-case basis. This refers not only to angiographic factors but also to patient factors. As mentioned earlier in this chapter, the use of DCB may facilitate a more abbreviated duration of DAPT, which may be attractive in high bleeding risk patients.

Repeat IVI after treatment should usually be performed to determine if an acceptable procedural result has been achieved. If not, further measures may be required to

optimize the result, and this process can be repeated until a satisfactory result is achieved.

For recurrent ISR, operators may find it useful to review the previous interventional procedure before managing the recurrence. Although this may not be possible in all cases, it may allow the operator to determine if relevant mechanical factors were identified and appropriately managed during the previous ISR treatment procedure. This may be particularly useful to avoid the vicious cycle of suboptimal ISR treatment, leading to an increased risk of recurrences, which can become increasingly challenging to manage.

FUTURE INTERVENTIONAL PARADIGMS

It has been suggested that the OCT ISR tissue pattern (classified based on the degree of ISR tissue homogeneity) could be used to guide the choice of therapeutic modality (DCB or DES).¹⁵¹ However, prospective RCTs are required to definitively determine whether the choice of DCB or DES therapy can be optimized based on OCT ISR tissue patterns, and this currently represents a gap in the scientific knowledge.

CONCLUSIONS

In-stent restenosis remains a significant issue in modern interventional cardiology practice, accounting for between 5% and 10% of all PCI procedures.

The underlying tissue substrate of ISR can encompass a wide pathophysiological spectrum, including vascular smooth muscle cell hyperplasia, proteoglycan-rich neointimal tissue, and neoatherosclerosis.

Although the management of ISR remains challenging, and optimal treatment algorithms have not been comprehensively defined, current evidence suggests that DES implantation or DCB angioplasty are the optimal treatment modalities for the majority of ISR cases. Regardless of the therapeutic modality used, tackling any stent underexpansion remains mandatory during these ISR PCI procedures.

Intravascular imaging can provide useful information to guide treatment decisions in ISR PCI, and further studies are required to determine if ISR interventional treatment paradigms can be guided by IVI ISR tissue patterns.

Visit Elsevier eBooks+ to access the complete list of references.

SELECTED REFERENCES

1. Alfonso Fernando F, Coughlan JJ, Giacoppo Daniele D, et al. Management of in-stent restenosis. *Euro Intervention*. 2022;18(2):e103-e123. doi:10.4244/EIJ-D-21-01034. In this issue.
2. Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol*. 2010;56(23):1897-1907.
3. Moussa ID, Mohanane D, Saucedo J, et al. Trends and outcomes of restenosis after coronary stent implantation in the United States. *J Am Coll Cardiol*. 2020;76(13):1521-1531.
4. Latib A, Mussardo M, Ielasi A, et al. Long-term outcomes after the percutaneous treatment of drug-eluting stent restenosis. *JACC Cardiovasc Interv*. 2011;4(2):155-164.

5. Assali AR, Moustapha A, Sdringola S, et al. Acute coronary syndrome may occur with in-stent restenosis and is associated with adverse outcomes (the PRESTO trial). *Am J Cardiol*. 2006;98(6):729-733.
6. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48(1):193-202.
7. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol*. 2011;57(11):1314-1322.
8. Otsuka F, Byrne RA, Yahagi K, et al. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. *Eur Heart J*. 2015;36(32):2147-2159.
9. Kang SJ, Mintz GS, Akasaka T, et al. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation*. 2011;123(25):2954-2963.
10. Habara M, Terashima M, Nasu K, et al. Morphological differences of tissue characteristics between early, late, and very late restenosis lesions after first generation drug-eluting stent implantation: an optical coherence tomography study. *Eur Heart J Cardiovasc Imaging*. 2013;14(3):276-284.
11. Taniwaki M, Windecker S, Zaugg S, et al. The association between in-stent neoatherosclerosis and native coronary artery disease progression: a long-term angiographic and optical coherence tomography cohort study. *Eur Heart J*. 2015;36(32):2167-2176.
12. Kastrati A, Schömig A, Dietz R, Neumann FJ, Richardt G. Time course of restenosis during the first year after emergency coronary stenting. *Circulation*. 1993;87(5):1498-1505.
13. Fujii K, Mintz GS, Kobayashi Y, et al. Contribution of stent underexpansion to recurrence after sirolimus-eluting stent implantation for in-stent restenosis. *Circulation*. 2004;109(9):1085-1078.
14. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation*. 1999;100(18):1872-1878.
15. Gonzalo N, Serruys PW, Okamura T, et al. Optical coherence tomography patterns of stent restenosis. *Am Heart J*. 2009;158(2):284-293.
16. Habara M, Terashima M, Nasu K, et al. Difference of tissue characteristics between early and very late restenosis lesions after bare-metal stent implantation: an optical coherence tomography study. *Circ Cardiovasc Interv*. 2011;4(3):232-238.
17. Giaccoppo D, Gargiulo G, Aruta P, Capranzano P, Tamburino C, Capodanno D. Treatment strategies for coronary in-stent restenosis: systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4880 patients. *BMJ*. 2015;351:h5392.
18. Siontis GC, Stefanini GG, Mavridis D, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. *Lancet*. 2015;386(9994):655-664.
19. Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med*. 2001;344(4):250-256.
20. Albiero R, Silber S, Di Mario C, et al. Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis: results of the restenosis cutting balloon evaluation trial (RESCUT). *J Am Coll Cardiol*. 2004;43(6):943-949.
21. Alfonso F, Zueco J, Cequier A, et al. A randomized comparison of repeat stenting with balloon angioplasty in patients with in-stent restenosis. *J Am Coll Cardiol*. 2003;42(5):796-805.
22. Hausleiter J, Kastrati A, Schömig A, Mehilli J, et al. Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis: the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial. *Circulation*. 2004;110(7):790-795.
23. Sharma SK, Kini A, Mehran R, Lansky A, Kobayashi Y, Marmur JD. Randomized trial of Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-stent Restenosis (ROSTER). *Am Heart J*. 2004;147(1):16-22.
24. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med*. 2006;355(20):2113-2124.
25. Alfonso F, Pérez-Vizcayno MJ, Hernandez R, et al. A randomized comparison of sirolimus-eluting stent with balloon angioplasty in patients with in-stent restenosis: results of the Restenosis Intra-stent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) trial. *J Am Coll Cardiol*. 2006;47(11):2152-2160.
26. Holmes DR Jr, Teirstein P, Satler L, et al. Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. *JAMA*. 2006;295(11):1264-1273.
27. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation*. 2009;119(23):2986-2994.
28. Mehilli J, Byrne RA, Tiroch K, et al. Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. *J Am Coll Cardiol*. 2010;55(24):2710-2716.
29. Wiemer M, König A, Rieber J, et al. Sirolimus-eluting stent implantation versus beta-irradiation for the treatment of in-stent restenotic lesions: clinical and ultrasound results from a randomised trial. *EuroIntervention*. 2011;6(6):687-694.
30. Rittger H, Brachmann J, Sinha AM, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. *J Am Coll Cardiol*. 2012;59(15):1377-1382.
31. Song HG, Park DW, Kim YH, et al. Randomized trial of optimal treatment strategies for in-stent restenosis after drug-eluting stent implantation. *J Am Coll Cardiol*. 2012;59(12):1093-1100.
32. Byrne RA, Neumann FJ, Mehilli J, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet*. 2013;381(9865):461-477.
33. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, et al. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V clinical trial (Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). *J Am Coll Cardiol*. 2014;63(14):1378-1386.
34. Xu B, Gao R, Wang J, et al. A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. *JACC Cardiovasc Interv*. 2014;7(2):204-211.
35. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, et al. A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: the RIBS IV randomized clinical trial. *J Am Coll Cardiol*. 2015;66(1):23-33.
36. Scheller B, Fontaine T, Mangner N, et al. A novel drug-coated scoring balloon for the treatment of coronary in-stent restenosis: results from the multicenter randomized controlled PATENT-C first in human trial. *Catheter Cardiovasc Interv*. 2016;88(1):51-59.
37. Pleva L, Kukla P, Kusnierova P, Zapletalova J, Hlinomaz O. Comparison of the efficacy of paclitaxel-eluting balloon catheters and everolimus-eluting stents in the treatment of coronary in-stent restenosis: the Treatment of In-Stent Restenosis study. *Circ Cardiovasc Interv*. 2016;9(4):e003316.
38. Kufner S, Joner M, Schneider S, et al. Neointimal modification with scoring balloon and efficacy of drug-coated balloon therapy in patients with restenosis in drug-eluting coronary stents: a randomized controlled trial. *JACC Cardiovasc Interv*. 2017;10(13):1332-1340.
39. Baan J Jr, Claessen BE, Dijk KB, et al. A randomized comparison of paclitaxel-eluting balloon versus everolimus-eluting stent for the treatment of any in-stent restenosis: the DARE trial. *JACC Cardiovasc Interv*. 2018;11(3):275-283.
40. Wong YTA, Kang DY, Lee JB, et al. Comparison of drug-eluting stents and drug-coated balloon for the treatment of drug-eluting coronary stent restenosis: a randomized RESTORE trial. *Am Heart J*. 2018;197:35-42.
41. Jensen CJ, Richardt G, Tölg R, et al. Angiographic and clinical performance of a paclitaxel-coated balloon compared to a second-generation sirolimus-eluting stent in patients with in-stent restenosis: the BIOLUX randomised controlled trial. *EuroIntervention*. 2018;14(10):1096-1103.
42. Chen Y, Gao L, Qin Q, et al. Comparison of 2 different drug-coated balloons in in-stent restenosis: the RESTORE ISR China randomized trial. *JACC Cardiovasc Interv*. 2018;11(23):2368-2377.
43. Ali RM, Abdul Kader M, Wan Ahmad WA, et al. treatment of coronary drug-eluting stent restenosis by a sirolimus- or paclitaxel-coated balloon. *JACC Cardiovasc Interv*. 2019;12(6):558-566.
44. Megaly M, Glogoz M, Xenogiannis I, et al. Coronary intravascular brachytherapy for recurrent coronary drug-eluting stent in-stent restenosis: a systematic review and meta-analysis. *Cardiovasc Revasc Med*. 2021;23:28-35.
45. Giaccoppo D, Alfonso F, Xu B, et al. Paclitaxel-coated balloon angioplasty vs. drug-eluting stenting for the treatment of coronary in-stent restenosis: a comprehensive, collaborative, individual patient data meta-analysis of 10 randomized clinical trials (DAEDALUS study). *Eur Heart J*. 2020;41(38):3715-3728.
46. Hamm CW, Dörr O, Woehle J, et al. A multicentre, randomised controlled clinical study of drug-coated balloons for the treatment of coronary in-stent restenosis. *EuroIntervention*. 2020;16(4):e328-e334.
47. Alfonso F, Pérez-Vizcayno MJ, García Del Blanco B, et al. Long-Term Results of Everolimus-Eluting Stents Versus Drug-Eluting Balloons in Patients With Bare-Metal In-Stent Restenosis: 3-Year Follow-Up of the RIBS V Clinical Trial. *JACC Cardiovasc Interv*. 2016;9(12):1246-1255.
48. Giaccoppo D, Alfonso F, Xu B, et al. Drug-coated balloon angioplasty versus drug-eluting stent implantation in patients with coronary stent restenosis. *J Am Coll Cardiol*. 2020;75(21):2664-2678.
49. Byrne RA, Cassese S, Windisch T, et al. Differential relative efficacy between drug-eluting stents in patients with bare metal and drug-eluting stent restenosis: evidence in support of drug resistance: insights from the ISAR-DESIRE and ISAR-DESIRE 2 trials. *EuroIntervention*. 2013;9(7):797-802.
50. Alfonso F, García J, Pérez-Vizcayno MJ, et al. New stent implantation for recurrences after stenting for in-stent restenosis: implications of a third metal layer in human coronary arteries. *J Am Coll Cardiol*. 2009;54(11):1036-1038.
51. Xhepa E, Bresha J, Joner M, et al. Clinical outcomes by optical characteristics of neointima and treatment modality in patients with coronary in-stent restenosis. *EuroIntervention*. 2021;17(5):e388-e395.

SUPPLEMENTAL MATERIAL

Search Strategy for Systematic Review

PubMed

((Coronary[Title/Abstract]) AND (In-Stent[Title/Abstract]))
AND (Restenosis[Title/Abstract])

Scopus

TITLE-ABS-KEY (coronary) AND TITLE-ABS-KEY (in-stent)
AND TITLE-ABS-KEY (restenosis) AND (LIMIT-TO (DOCTYPE,
"ar") OR LIMIT-TO (DOCTYPE, "le")) AND (LIMIT-TO (SUB-
JAREA, "MEDI")) AND (LIMIT-TO (SRCTYPE, "j") OR LIMIT-TO
(SRCTYPE, "p"))

Web of Science

((TS=(Coronary)) OR TI=(Coronary)) OR AB=(Coronary)
((TS=(In-Stent)) OR TI=(In-Stent)) OR AB=(In-Stent)

((TS=(Restenosis)) OR TI=(Restenosis)) OR AB=(Restenosis)
#1 AND #2 AND #3

Document Type: Articles or Proceedings Paper or Meeting
Abstracts

Ovid

(Coronary and In-Stent and Restenosis).ti,ab,kw.

1 and "Clinical Trial" [Publication Type]

1 and "Randomized Controlled Trial" [Publication Type]

1 and "Comparative Study" [Publication Type]

1 and "Clinical Study" [Publication Type]

1 and "Controlled Clinical Trial" [Publication Type]

2 or 3 or 4 or 5

All resources

REFERENCES

1. Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol*. 2010;56(23):1897-907.
2. Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. *J Am Coll Cardiol*. 2014;63(24):2659-2673.
3. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007;356(10):1030-1039.
4. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet*. 2007;370(9591):937-948.
5. Moussa ID, Mohanany D, Saucedo J, et al. Trends and outcomes of restenosis after coronary stent implantation in the United States. *J Am Coll Cardiol*. 2020;76(13):1521-1531.
6. Alfonso F, Kastrati A. Clinical burden and implications of coronary interventions for in-stent restenosis. *EuroIntervention*. 2021;17(5):e355-e357.
7. Kufner S, Ernst M, Cassese S, et al. 10-year outcomes from a randomized trial of polymer-free versus durable polymer drug-eluting coronary stents. *J Am Coll Cardiol*. 2020;76(2):146-158.
8. Kastrati A, Byrne R. New roads, new ruts: lessons from drug-eluting stent restenosis. *JACC Cardiovasc Interv*. 2011;4(2):165-167.
9. Latib A, Mussardo M, Ielasi A, et al. Long-term outcomes after the percutaneous treatment of drug-eluting stent restenosis. *JACC Cardiovasc Interv*. 2011;4(2):155-164.
10. Assali AR, Moustapha A, Sdringola S, et al. Acute coronary syndrome may occur with in-stent restenosis and is associated with adverse outcomes (the PRESTO trial). *Am J Cardiol*. 2006;98(6):729-733.
11. Kuntz RE, Baim DS. Defining coronary restenosis. Newer clinical and angiographic paradigms. *Circulation*. 1993;88(3):1310-1323.
12. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Gruntzig Lecture ESC 2014. *Eur Heart J*. 2015;36(47):3320-3331.
13. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48(1):193-202.
14. Nakano M, Otsuka F, Yahagi K, et al. Human autopsy study of drug-eluting stents restenosis: histomorphological predictors and neointimal characteristics. *Eur Heart J*. 2013;34(42):3304-3313.
15. Carrabba N, Schuijff JD, de Graaf FR, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography for the detection of in-stent restenosis: a meta-analysis. *J Nucl Cardiol*. 2010;17(3):470-478.
16. Costa MA, Simon DI. Molecular basis of restenosis and drug-eluting stents. *Circulation*. 2005;111(17):2257-2273.
17. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol*. 2011;57(11):1314-1322.
18. Otsuka F, Byrne RA, Yahagi K, et al. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. *Eur Heart J*. 2015;36(32):2147-2159.
19. Byrne RA, Joner M, Tada T, Kastrati A. Restenosis in bare metal and drug-eluting stents: distinct mechanistic insights from histopathology and optical intravascular imaging. *Minerva Cardioangiol*. 2012;60(5):473-489.
20. Goto K, Zhao Z, Matsumura M, et al. Mechanisms and patterns of intravascular ultrasound in-stent restenosis among bare metal stents and first- and second-generation drug-eluting stents. *Am J Cardiol*. 2015;116(9):1351-1357.
21. Kang SJ, Mintz GS, Akasaka T, et al. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation*. 2011;123(25):2954-2963.
22. Habara M, Terashima M, Nasu K, et al. Morphological differences of tissue characteristics between early, late, and very late restenosis lesions after first generation drug-eluting stent implantation: an optical coherence tomography study. *Eur Heart J Cardiovasc Imaging*. 2013;14(3):276-284.
23. Kilickesmez K, Dall'Ara G, Rama-Merchan JC, et al. Optical coherence tomography characteristics of in-stent restenosis are different between first and second generation drug eluting stents. *Int J Cardiol Heart Vessel*. 2014;3:68-74.
24. Taniwaki M, Windecker S, Zaugg S, et al. The association between in-stent neoatherosclerosis and native coronary artery disease progression: a long-term angiographic and optical coherence tomography cohort study. *Eur Heart J*. 2015;36(32):2167-2176.
25. Kastrati A, Schömig A, Dietz R, Neumann FJ, Richardt G. Time course of restenosis during the first year after emergency coronary stenting. *Circulation*. 1993;87(5):1498-1505.
26. Kimura T, Nosaka H, Yokoi H, Iwabuchi M, Nobuyoshi M. Serial angiographic follow-up after Palmaz-Schatz stent implantation: comparison with conventional balloon angioplasty. *J Am Coll Cardiol*. 1993;21(7):1557-1563.
27. Räber L, Wohlwend L, Wigger M, et al. Five-year clinical and angiographic outcomes of a randomized comparison of sirolimus-eluting and paclitaxel-eluting stents: results of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial. *Circulation*. 2011;123(24):2819-2828.
28. Byrne RA, Iijima R, Mehilli J, et al. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. *JACC Cardiovasc Interv*. 2009;2(4):291-299.
29. Shlofmitz E, Iantorno M, Waksman R. Restenosis of drug-eluting stents: a new classification system based on disease mechanism to guide treatment and state-of-the-art review. *Circ Cardiovasc Interv*. 2019;12(8):e007023.
30. Fujii K, Mintz GS, Kobayashi Y, et al. Contribution of stent underexpansion to recurrence after sirolimus-eluting stent implantation for in-stent restenosis. *Circulation*. 2004;109(9):1085-1078.
31. Yin D, Mintz GS, Song L, et al. In-stent restenosis characteristics and repeat stenting underexpansion: insights from optical coherence tomography. *EuroIntervention*. 2020;16(4):e335-e343.
32. Alfonso Fernando F, Coughlan JJ, Giacoppo Daniele D, et al. Management of in-stent restenosis. *Euro Intervention*. 2022;18(2):e103-e123. doi:10.4244/EIJ-D-21-01034. In this issue.
33. Kang SJ, Mintz GS, Park DW, et al. Mechanisms of in-stent restenosis after drug-eluting stent implantation: intravascular ultrasound analysis. *Circ Cardiovasc Interv*. 2011;4(1):9-14.
34. Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J*. 2006;151(6):1260-1264.
35. Magalhaes MA, Minha S, Chen F, et al. Clinical presentation and outcomes of coronary in-stent restenosis across 3-stent generations. *Circ Cardiovasc Interv*. 2014;7(6):768-776.
36. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation*. 1999;100(18):1872-1878.
37. Solinas E, Dangas G, Kirtane AJ, et al. Angiographic patterns of drug-eluting stent restenosis and one-year outcomes after treatment with repeated percutaneous coronary intervention. *Am J Cardiol*. 2008;102(3):311-315.
38. Räber L, Mintz GS, Koskinas KC, et al. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J*. 2018;39(35):3281-3300.
39. Alfonso F, Sandoval J, Cárdenas A, Medina M, Cuevas C, Gonzalo N. Optical coherence tomography: from research to clinical application. *Minerva Med*. 2012;103(6):441-464.
40. Koskinas KC, Nakamura M, Räber L, et al. Current use of intracoronary imaging in interventional practice—results of a European Association of Percutaneous Cardiovascular Interventions (EAPCI) and Japanese Association of Cardiovascular Interventions and Therapeutics (CVIT) Clinical Practice Survey. *EuroIntervention*. 2018;14(4):e475-e484.
41. Malle C, Tada T, Steigerwald K, et al. Tissue characterization after drug-eluting stent implantation using optical coherence tomography. *Arterioscler Thromb Vasc Biol*. 2013;33(6):1376-1383.
42. Gonzalo N, Serruys PW, Okamura T, et al. Optical coherence tomography patterns of stent restenosis. *Am Heart J*. 2009;158(2):284-293.
43. Habara M, Terashima M, Nasu K, et al. Difference of tissue characteristics between early and very late restenosis lesions after bare-metal stent implantation: an optical coherence tomography study. *Circ Cardiovasc Interv*. 2011;4(3):232-238.
44. Kim JS, Afari ME, Ha J, et al. Neointimal patterns obtained by optical coherence tomography correlate with specific histological components and neointimal proliferation in a swine model of restenosis. *Eur Heart J Cardiovasc Imaging*. 2014;15(3):292-298.
45. Tada T, Kadota K, Hosogi S, et al. Association between tissue characteristics assessed with optical coherence tomography and mid-term results after percutaneous coronary intervention for in-stent restenosis lesions: a comparison between balloon angioplasty, paclitaxel-coated balloon dilatation, and drug-eluting stent implantation. *Eur Heart J Cardiovasc Imaging*. 2015;16(10):1101-1111.
46. Lopez-Palop R, Pinar E, Lozano I, Saura D, Picó F, Valdés M. Utility of the fractional flow reserve in the evaluation of angiographically moderate in-stent restenosis. *Eur Heart J*. 2004;25(22):2040-2047.
47. Miura K, Tada T, Habara S, et al. Optical coherence tomography predictors for recurrent restenosis after paclitaxel-coated balloon angioplasty for drug-eluting stent restenosis. *Circ J*. 2018;82(11):2820-2828.
48. Giacoppo D, Gargiulo G, Aruta P, Capranzano P, Tamburino C, Capodanno D. Treatment strategies for coronary in-stent restenosis: systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4880 patients. *BMJ*. 2015;351:h5392.
49. Siontis GC, Stefanini GG, Mavridis D, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. *Lancet*. 2015;386(9994):655-664.
50. Teirstein PS, Massullo V, Jani S, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med*. 1997;336(24):1697-1703.
51. Waksman R, Bhargava B, White L, et al. Intracoronary beta-radiation therapy inhibits recurrence of in-stent restenosis. *Circulation*. 2000;101(16):1895-1898.
52. Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med*. 2001;344(4):250-256.
53. vom Dahl J, Dietz U, Haager PK, et al. Rotational atherectomy does not reduce recurrent restenosis: results of the angioplasty versus rotational atherectomy for treatment of diffuse in-stent restenosis trial (ARTIST). *Circulation*. 2002;105(5):583-588.
54. Albiero R, Silber S, Di Mario C, et al. Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis: results of the restenosis cutting balloon evaluation trial (RESCUT). *J Am Coll Cardiol*. 2004;43(6):943-949.
55. Alfonso F, Zueco J, Cequier A, et al. A randomized comparison of repeat stenting with balloon angioplasty in patients with in-stent restenosis. *J Am Coll Cardiol*. 2003;42(5):796-805.
56. Waksman R, Cheneau E, Ajani AE, et al. Intracoronary radiation therapy improves the clinical and angiographic outcomes of diffuse in-stent restenotic lesions: results of the Washington Radiation for In-Stent Restenosis Trial for Long Lesions (Long WRIST) Studies. *Circulation*. 2003;107(13):1744-1749.
57. Hausleiter J, Kastrati A, Mehilli J, et al. Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with

- in-stent restenosis: the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial. *Circulation*. 2004;110(7):790-795.
58. Ragosta M, Samady H, Gimple LW, Sarembock IJ, Fenster M, Powers ER. Percutaneous treatment of focal vs. diffuse in-stent restenosis: a prospective randomized comparison of conventional therapies. *Catheter Cardiovasc Interv*. 2004;61(3):344-349.
 59. Montorsi P, Galli S, Fabbicchi F, Trabattini D, Ravagnani PM, Bartorelli AL. Randomized trial of conventional balloon angioplasty versus cutting balloon for in-stent restenosis. Acute and 24-hour angiographic and intravascular ultrasound changes and long-term follow-up. *Ital Heart J*. 2004;5(4):271-279.
 60. Sharma SK, Kini A, Mehran R, Lansky A, Kobayashi Y, Marmur JD. Randomized trial of Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-stent Restenosis (ROSTER). *Am Heart J*. 2004;147(1):16-22.
 61. Alfonso F, García P, Fleites H, et al. Repeat stenting for the prevention of the early lumen loss phenomenon in patients with in-stent restenosis. Angiographic and intravascular ultrasound findings of a randomized study. *Am Heart J*. 2005;149(2):e1-e8.
 62. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA*. 2005;293(2):165-171.
 63. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med*. 2006;355(20):2113-2124.
 64. Alfonso F, Pérez-Vizcayno MJ, Hernandez R, et al. A randomized comparison of sirolimus-eluting stent with balloon angioplasty in patients with in-stent restenosis: results of the Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) trial. *J Am Coll Cardiol*. 2006;47(11):2152-2160.
 65. Holmes DR Jr, Teirstein P, Satler L, et al. Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. *JAMA*. 2006;295(11):1264-1273.
 66. Stone GW, Ellis SG, O'Shaughnessy CD, et al. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. *JAMA*. 2006;295(11):1253-1263.
 67. Park SW, Lee SW, Koo BK, et al. Treatment of diffuse in-stent restenosis with drug-eluting stents vs. intracoronary beta-radiation therapy: INDEED Study. *Int J Cardiol*. 2008;131(1):70-77.
 68. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation*. 2009;119(23):2986-2994.
 69. Mehilli J, Byrne RA, Tiroch K, et al. Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. *J Am Coll Cardiol*. 2010;55(24):2710-2716.
 70. Habara S, Mitsudo K, Kadota K, et al. Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. *JACC Cardiovasc Interv*. 2011;4(2):149-154.
 71. Wiemer M, König A, Rieber J, et al. Sirolimus-eluting stent implantation versus beta-irradiation for the treatment of in-stent restenotic lesions: clinical and ultrasound results from a randomised trial. *EuroIntervention*. 2011;6(6):687-694.
 72. Rittger H, Brachmann J, Sinha AM, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. *J Am Coll Cardiol*. 2012;59(15):1377-1382.
 73. Song HG, Park DW, Kim YH, et al. Randomized trial of optimal treatment strategies for in-stent restenosis after drug-eluting stent implantation. *J Am Coll Cardiol*. 2012;59(12):1093-1100.
 74. Chevalier B, Moulichon R, Teiger E, et al. One-year results of the CRISTAL Trial, a randomized comparison of cypher sirolimus-eluting coronary stents versus balloon angioplasty for restenosis of drug-eluting stents. *J Interv Cardiol*. 2012;25(6):586-595.
 75. Byrne RA, Neumann FJ, Mehilli J, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet*. 2013;381(9865):461-477.
 76. Habara S, Iwabuchi M, Inoue N, et al. A multicenter randomized comparison of paclitaxel-coated balloon catheter with conventional balloon angioplasty in patients with bare-metal stent restenosis and drug-eluting stent restenosis. *Am Heart J*. 2013;166(3):527-533.
 77. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, et al. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V clinical trial (Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). *J Am Coll Cardiol*. 2014;63(14):1378-1386.
 78. Xu B, Gao R, Wang J, et al. A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. *JACC Cardiovasc Interv*. 2014;7(2):204-211.
 79. Adriaenssens T, Dens J, Ughi G, et al. Optical coherence tomography study of healing characteristics of paclitaxel-eluting balloons vs. everolimus-eluting stents for in-stent restenosis: the SEDUCE (Safety and Efficacy of a Drug eluting balloon in Coronary artery rEstenosis) randomised clinical trial. *EuroIntervention*. 2014;10(4):439-448.
 80. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, et al. A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: the RIBS IV randomized clinical trial. *J Am Coll Cardiol*. 2015;66(1):23-33.
 81. Scheller B, Fontaine T, Mangner N, et al. A novel drug-coated scoring balloon for the treatment of coronary in-stent restenosis: results from the multi-center randomized controlled PATENT-C first in human trial. *Catheter Cardiovasc Interv*. 2016;88(1):51-59.
 82. Pleva L, Kukla P, Kusnierova P, Zapletalova J, Hlinomaz O. Comparison of the efficacy of paclitaxel-eluting balloon catheters and everolimus-eluting stents in the treatment of coronary in-stent restenosis: the Treatment of In-Stent Restenosis study. *Circ Cardiovasc Interv*. 2016;9(4):e003316.
 83. Hong SJ, Ahn CM, Kim BK, et al. Prospective randomized comparison of clinical and angiographic outcomes between everolimus-eluting vs. zotarolimus-eluting stents for treatment of coronary restenosis in drug-eluting stents: intravascular ultrasound volumetric analysis (RESTENT-ISR trial). *Eur Heart J*. 2016;37(45):3409-3418.
 84. Kufner S, Joner M, Schneider S, et al. Neointimal modification with scoring balloon and efficacy of drug-coated balloon therapy in patients with restenosis in drug-eluting coronary stents: a randomized controlled trial. *JACC Cardiovasc Interv*. 2017;10(13):1332-1340.
 85. Baan J Jr, Claessen BE, Dijk KB, et al. A randomized comparison of paclitaxel-eluting balloon versus everolimus-eluting stent for the treatment of any in-stent restenosis: the DARE trial. *JACC Cardiovasc Interv*. 2018;11(3):275-283.
 86. Wong YTA, Kang DY, Lee JB, et al. Comparison of drug-eluting stents and drug-coated balloon for the treatment of drug-eluting coronary stent restenosis: a randomized RESTORE trial. *Am Heart J*. 2018;197:35-42.
 87. Jensen CJ, Richardt G, Tölg R, et al. Angiographic and clinical performance of a paclitaxel-coated balloon compared to a second-generation sirolimus-eluting stent in patients with in-stent restenosis: the BILUX randomised controlled trial. *EuroIntervention*. 2018;14(10):1096-1103.
 88. Chen Y, Gao L, Qin Q, et al. Comparison of 2 different drug-coated balloons in in-stent restenosis: the RESTORE ISR China randomized trial. *JACC Cardiovasc Interv*. 2018;11(23):2368-2377.
 89. Ali RM, Abdul Kader M, Wan Ahmad WA, et al. treatment of coronary drug-eluting stent restenosis by a sirolimus- or paclitaxel-coated balloon. *JACC Cardiovasc Interv*. 2019;12(6):558-566.
 90. Aoki J, Nakazawa G, Ando K, et al. Effect of combination of non-slip element balloon and drug-coating balloon for in-stent restenosis lesions (ELEGANT study). *J Cardiol*. 2019;74(5):436-442.
 91. Sato T, Tsuchida K, Yuasa S, et al. The effect of the debulking by excimer laser coronary angioplasty on long-term outcome compared with drug-coating balloon: insights from optical frequency domain imaging analysis. *Lasers Med Sci*. 2020;35(2):403-412.
 92. Mehran R, Mintz GS, Popma JJ, et al. Mechanisms and results of balloon angioplasty for the treatment of in-stent restenosis. *Am J Cardiol*. 1996;78(6):618-622.
 93. Raja Y, Routledge HC, Doshi SN. A noncompliant, high pressure balloon to manage undilatable coronary lesions. *Catheter Cardiovasc Interv*. 2010;75(7):1067-1073.
 94. Alfonso F, Pérez-Vizcayno MJ, Gómez-Recio M, et al. Implications of the "watermelon seeding" phenomenon during coronary interventions for in-stent restenosis. *Catheter Cardiovasc Interv*. 2005;66(4):521-527.
 95. Mintz GS, Hoffmann R, Mehran R, et al. In-stent restenosis: the Washington Hospital Center experience. *Am J Cardiol*. 1998;81(7a):7e-13e.
 96. Gruberg L, Waksman R. Intravascular radiation for the prevention of recurrence of restenosis in coronary arteries. *Expert Opin Investig Drugs*. 2001;10(5):891-907.
 97. Waksman R, Robinson KA, Crocker IR, Gravanis MB, Cipolla GD, King SB 3rd. Endovascular low-dose irradiation inhibits neointima formation after coronary artery balloon injury in swine. A possible role for radiation therapy in restenosis prevention. *Circulation*. 1995;91(5):1533-1539.
 98. Waksman R, Robinson KA, Crocker IR, et al. Intracoronary low-dose beta-irradiation inhibits neointima formation after coronary artery balloon injury in the swine restenosis model. *Circulation*. 1995;92(10):3025-3031.
 99. Waksman R, White RL, Chan RC, et al. Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. *Circulation*. 2000;101(18):2165-2171.
 100. Popma JJ, Suntharalingam M, Lansky AJ, et al. Randomized trial of 90Sr/90Y beta-radiation versus placebo control for treatment of in-stent restenosis. *Circulation*. 2002;106(9):1090-1096.
 101. Waksman R, Raizner AE, Yeung AC, Lansky AJ, Vandertie L. Use of localised intracoronary beta radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. *Lancet*. 2002;359(9306):551-5517.
 102. Sabaté M, Costa MA, Kozuma K, et al. Geographic miss: a cause of treatment failure in radio-oncology applied to intracoronary radiation therapy. *Circulation*. 2000;101(21):2467-2471.
 103. Waksman R, Ajani AE, Pinnow E, et al. Twelve versus six months of clopidogrel to reduce major cardiac events in patients undergoing gamma-radiation therapy for in-stent restenosis: Washington Radiation for In-Stent restenosis Trial (WRIST) 12 versus WRIST PLUS. *Circulation*. 2002;106(7):776-778.
 104. Negi SI, Torguson R, Gai J, et al. Intracoronary brachytherapy for recurrent drug-eluting stent failure. *JACC Cardiovasc Interv*. 2016;9(12):1259-1265.
 105. Megaly M, Glogoz M, Xenogiannis I, et al. Coronary intravascular brachytherapy for recurrent coronary drug-eluting stent in-stent restenosis: a systematic review and meta-analysis. *Cardiovasc Rev Med*. 2021;23:28-35.
 106. Kobayashi Y, Teirstein P, Linnemeier T, Stone G, Leon M, Moses J. Rotational atherectomy (stentablation) in a lesion with stent underexpansion



- due to heavily calcified plaque. *Catheter Cardiovasc Interv.* 2001;52(2):208-211.
107. Alfonso F, Sandoval J, Nolte C. Calcified in-stent restenosis: a rare cause of dilation failure requiring rotational atherectomy. *Circ Cardiovasc Interv.* 2012;5(1):e1-e2.
108. Bastante T, Rivero F, Cuesta J, Alfonso F. Calcified neoatherosclerosis causing "undilatable" in-stent restenosis: insights of optical coherence tomography and role of rotational atherectomy. *JACC Cardiovasc Interv.* 2015;8(15):2039-2040.
109. Takano M, Yamamoto M, Murakami D, et al. Optical coherence tomography after new scoring balloon angioplasty for in-stent restenosis and de novo coronary lesions. *Int J Cardiol.* 2010;141(3):e51-e53.
110. Fasseas P, Orford JL, Lennon R, et al. Cutting balloon angioplasty vs. conventional balloon angioplasty in patients receiving intracoronary brachytherapy for the treatment of in-stent restenosis. *Catheter Cardiovasc Interv.* 2004;63(2):152-157.
111. Kufner S, Hausleiter J, Ndrepepa G, et al. Long-term risk of adverse outcomes and new malignancies in patients treated with oral sirolimus for prevention of restenosis. *JACC Cardiovasc Interv.* 2009;2(11):1142-1148.
112. Giacoppo D, Alfonso F, Xu B, et al. Paclitaxel-coated balloon angioplasty vs. drug-eluting stenting for the treatment of coronary in-stent restenosis: a comprehensive, collaborative, individual patient data meta-analysis of 10 randomized clinical trials (DAEDALUS study). *Eur Heart J.* 2020;41(38):3715-3728.
113. Alfonso F, Pérez-Vizcayno MJ, Dutary J, et al. Implantation of a drug-eluting stent with a different drug (switch strategy) in patients with drug-eluting stent restenosis. Results from a prospective multicenter study (RIBS III [Restenosis Intra-Stent: Balloon Angioplasty Versus Drug-Eluting Stent]). *JACC Cardiovasc Interv.* 2012;5(7):728-737.
114. Vyas A, Schweizer M, Malhotra A, Karrowni W. Meta-analysis of same versus different stent for drug-eluting stent restenosis. *Am J Cardiol.* 2014;113(4):601-606.
115. Radke PW, Joner M, Joost A, et al. Vascular effects of paclitaxel following drug-eluting balloon angioplasty in a porcine coronary model: the importance of excipients. *EuroIntervention.* 2011;7(6):730-737.
116. Hamm CW, Dörr O, Woehle J, et al. A multicentre, randomised controlled clinical study of drug-coated balloons for the treatment of coronary in-stent restenosis. *EuroIntervention.* 2020;16(4):e328-e334.
117. Rittger H, Waliszewski M, Brachmann J, et al. Long-term outcomes after treatment with a paclitaxel-coated balloon versus balloon angioplasty: insights from the PEPCAD-DES study (Treatment of Drug-eluting Stent [DES] In-Stent Restenosis With SeQuent Please Paclitaxel-Coated Percutaneous Transluminal Coronary Angioplasty [PTCA] Catheter). *JACC Cardiovasc Interv.* 2015;8(13):1695-1700.
118. Colleran R, Joner M, Kufner S, et al. Comparative efficacy of two paclitaxel-coated balloons with different excipient coatings in patients with coronary in-stent restenosis: a pooled analysis of the Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-Stent Restenosis 3 and 4 (ISAR-DESIRE 3 and ISAR-DESIRE 4) trials. *Int J Cardiol.* 2018;252:57-62.
119. Kufner S, Rai H, Wiebe J, et al. A prospective trial of a novel low-dose paclitaxel-coated balloon therapy in patients with restenosis in drug-eluting coronary stents Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-stent REstenosis 3A (ISAR-DESIRE 3A). *Catheter Cardiovasc Interv.* 2022;99(3):754-762.
120. Scheller B, Vukadinovic D, Jeger R, et al. survival after coronary revascularization with paclitaxel-coated balloons. *J Am Coll Cardiol.* 2020;75(9):1017-1028.
121. Cortese B, di Palma G, Latini RA, Elwany M, Orrego PS, Seregni RG. Immediate and short-term performance of a novel sirolimus-coated balloon during complex percutaneous coronary interventions. The FAtenefratelli Sirolimus COated-balloon (FASICO) registry. *Cardiovasc Revasc Med.* 2017;18(7):487-491.
122. Verheye S, Vrolix M, Kumsars I, et al. The SABRE Trial (Sirolimus Angioplasty Balloon for Coronary In-Stent Restenosis): angiographic results and 1-year clinical outcomes. *JACC Cardiovasc Interv.* 2017;10(20):2029-2037.
123. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis: the three-year results of the PEPCAD II ISR study. *EuroIntervention.* 2015;11(8):926-934.
124. Alfonso F, Pérez-Vizcayno MJ, García Del Blanco B, et al. Comparison of the Efficacy of Everolimus-Eluting Stents Versus Drug-Eluting Balloons in Patients With In-Stent Restenosis (from the RIBS IV and V Randomized Clinical Trials). *Am J Cardiol.* 2016;117(4):546-554.
125. Alfonso F, Pérez-Vizcayno MJ, García Del Blanco B, et al. Long-Term Results of Everolimus-Eluting Stents Versus Drug-Eluting Balloons in Patients With Bare-Metal In-Stent Restenosis: 3-Year Follow-Up of the RIBS V Clinical Trial. *JACC Cardiovasc Interv.* Jun 27 2016;9(12):1246-1255.
126. Alfonso F, Pérez-Vizcayno MJ, Cuesta J, et al. 3-year clinical follow-up of the RIBS IV clinical trial: a prospective randomized study of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis in coronary arteries previously treated with drug-eluting stents. *JACC Cardiovasc Interv.* 2018;11(10):981-991.
127. Alfonso F, Pérez-Vizcayno MJ, García Del Blanco B, et al. Usefulness of Drug-Eluting Balloons for Bare-Metal and Drug-Eluting In-Stent Restenosis (from the RIBS IV and V Randomized Trials). *Am J Cardiol.* 2017;119(7):983-990.
128. Giacoppo D, Alfonso F, Xu B, et al. Drug-coated balloon angioplasty versus drug-eluting stent implantation in patients with coronary stent restenosis. *J Am Coll Cardiol.* 2020;75(21):2664-2678.
129. Byrne RA, Cassese S, Windisch T, et al. Differential relative efficacy between drug-eluting stents in patients with bare metal and drug-eluting stent restenosis; evidence in support of drug resistance: insights from the ISAR-DESIRE and ISAR-DESIRE 2 trials. *EuroIntervention.* 2013;9(7):797-802.
130. Alfonso F, Cuesta J, Pérez-Vizcayno MJ, et al. Bioresorbable vascular scaffolds for patients with in-stent restenosis: the RIBS VI study. *JACC Cardiovasc Interv.* 2017;10(18):1841-1851.
131. Alfonso F, Cuesta J, García Del Blanco B, et al. Scoring balloon predilation before bioresorbable vascular scaffold implantation in patients with in-stent restenosis: the RIBS VI "scoring" study. *Coron Artery Dis.* 2021;32(2):96-104.
132. Ali ZA, Serruys PW, Kimura T, et al. 2-year outcomes with the Absorb bioresorbable scaffold for treatment of coronary artery disease: a systematic review and meta-analysis of seven randomised trials with an individual patient data substudy. *Lancet.* 2017;390(10096):760-772.
133. Alfonso F, Cuesta J, García-Guimaraes M, Bastante T, Maruri R, Rivero F. Treatment of coronary stent restenosis with drug-eluting bioabsorbable magnesium scaffolds. *Coron Artery Dis.* 2017;28(7):627-628.
134. Alfonso F, Cuesta J, García-Guimaraes M, Rivero F. "Bumpy" neointima: the fingerprint of bioabsorbable magnesium scaffold resorption. *EuroIntervention.* 2019;15(4):e380-e381.
135. Alfonso F, Cuesta J, Ojeda S, et al. Procedural Results and One-Year Clinical Outcomes of Treatment of Bioresorbable Vascular Scaffolds Restenosis (from the RIBS VII Prospective Study). *Am J Cardiol.* 2022;162:31-40.
136. Egred M, Brilakis ES. Excimer laser coronary angioplasty (ELCA): fundamentals, mechanism of action, and clinical applications. *J Invasive Cardiol.* 2020;32(2):E27-E35.
137. Tsutsui RS, Sammour Y, Kalra A, et al. Excimer laser atherectomy in percutaneous coronary intervention: a contemporary review. *Cardiovasc Revasc Med.* 2021;25:75-85.
138. Mehran R, Dangas G, Mintz GS, et al. Treatment of in-stent restenosis with excimer laser coronary angioplasty versus rotational atherectomy: comparative mechanisms and results. *Circulation.* 2000;101(21):2484-2489.
139. Hill JM, Kereiakes DJ, Shlofmitz RA, et al. Intravascular lithotripsy for treatment of severely calcified coronary artery disease. *J Am Coll Cardiol.* 2020;76(22):2635-2646.
140. Kereiakes DJ, Di Mario C, Riley RF, et al. intravascular lithotripsy for treatment of calcified coronary lesions: patient-level pooled analysis of the Disrupt CAD studies. *JACC Cardiovasc Interv.* 2021;14(12):1337-1348.
141. Nikolakopoulos I, Vemou E, Xenogiannis I, Brilakis ES. Combined use of intravascular lithotripsy and brachytherapy: a new approach for the treatment of recurrent coronary in-stent restenosis. *Catheter Cardiovasc Interv.* 2021;97(7):1402-1406.
142. Salazar C, Escaned J, Tirado G, Gonzalo N. Intravascular lithotripsy for recurrent restenosis caused by severe calcific neoatherosclerosis. *EuroIntervention.* 2020;16(4):e351-e352.
143. Tizón-Marcos H, Rodríguez-Costoya I, Tevar C, Vaquerizo B. Intracoronary lithotripsy for calcific neoatherosclerotic in-stent restenosis: a case report. *Eur Heart J Case Rep.* 2020;4(4):1-4.
144. Brunner FJ, Becher PM, Waldeyer C, et al. Intravascular lithotripsy for the treatment of calcium-mediated coronary in-stent restenoses. *J Invasive Cardiol.* 2021;33(1):E25-E31.
145. Alfonso F, Bastante T, Antuña P, et al. Coronary lithoplasty for the treatment of undilatable calcified de novo and in-stent restenosis lesions. *JACC Cardiovasc Interv.* 2019;12(5):497-499.
146. Alfonso F, García J, Pérez-Vizcayno MJ, et al. New stent implantation for recurrences after stenting for in-stent restenosis: implications of a third metal layer in human coronary arteries. *J Am Coll Cardiol.* 2009;54(11):1036-1038.
147. Martin JL, Ellis SG, Colombo A, et al. Frequency of coronary artery bypass grafting following implantation of a paclitaxel-eluting or a bare-metal stent into a single coronary artery. *Am J Cardiol.* 2009;103(1):11-16.
148. Moustapha A, Assali AR, Sdringola S, et al. Percutaneous and surgical interventions for in-stent restenosis: long-term outcomes and effect of diabetes mellitus. *J Am Coll Cardiol.* 2001;37(7):1877-1882.
149. Kanemitsu S, Tanaka K, Tanaka J, Suzuki H, Kinoshita T. Coronary artery bypass grafting following in-stent restenosis of drug-eluting stents deployed in the left main coronary artery. *Circ J.* 2008;72(3):502-504.
150. Mishell JM, Vakharia KT, Ports TA, Yeghiazarians Y, Michaels AD. Determination of adequate coronary stent expansion using StentBoost, a novel fluoroscopic image processing technique. *Catheter Cardiovasc Interv.* 2007;69(1):84-93.
151. Xhepa E, Bresha J, Joner M, et al. Clinical outcomes by optical characteristics of neointima and treatment modality in patients with coronary in-stent restenosis. *EuroIntervention.* 2021;17(5):e388-e395.



14 Management Of Thrombotic Lesions

ANTHONY A. BAVRY

INTRODUCTION, 256

PHARMACOLOGIC STRATEGIES TO PREVENT THROMBUS FORMATION, 256

THROMBUS IN VARIOUS CLINICAL SCENARIOS, 257

Thrombus from de Novo Plaque Rupture, 257

Coronary Embolism, 258

Stent Thrombosis, 258

Bypass Graft Thrombosis, 258

DEVICES TO REMOVE THROMBUS, 258

Simple Aspiration Thrombectomy, 258

Mechanical Aspiration Thrombectomy, 258

EXPERIMENTAL DEVICES, 260

DEVICES THAT ARE NOT BENEFICIAL, 261

CASE, 261

CONCLUSIONS, 261

INTRODUCTION

Thrombus prevention and management represent a core interventional cardiology topic. Thrombus can form at any time during coronary revascularization, thus complicating percutaneous coronary intervention (PCI). This complication can occur among patients with both stable and unstable coronary artery disease; however, it is more likely to occur among the latter. Prevention of thrombus formation during revascularization largely centers on pharmacologic strategies, which include antiplatelet and antithrombin medications. An understanding of thrombogenesis and strategies to prevent thrombus formation is crucial for the safe and successful conduct of PCI.

In addition to a potential complication during PCI, thrombus can also be encountered de novo during non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI); therefore, strategies to manage formed thrombus are also necessary. Thrombus causing an acute coronary syndrome (ACS) can occur from native coronary artery plaque rupture, coronary embolization, stent thrombosis, and bypass graft thrombosis. Much of the management of formed thrombus centers on mechanical devices to extract or remove the thrombus from the coronary artery without causing embolization into the microcirculation, although pharmacologic therapy remains important.

This chapter reviews the current pharmacologic approaches to prevent thrombus formation and mechanical approaches to extract formed thrombus from the coronary artery.

PHARMACOLOGIC STRATEGIES TO PREVENT THROMBUS FORMATION

Interventional cardiology has long been a balance of preventing of thrombus formation during PCI without causing excessing bleeding. Pharmacologic strategies can be grouped into antithrombin and antiplatelet agents. After the decision has been made to perform PCI, an antithrombin agent is selected and administered. Options for antithrombin agents include unfractionated heparin (UFH),

bivalirudin (i.e., Angiomax), or low-molecular-weight heparin (LMWH; i.e., enoxaparin). UFH is given weight-based to achieve an activated clotting time (ACT) longer than 250 to 300 seconds. Bivalirudin has been extensively studied and is an acceptable alternative agent to UFH (class of recommendation 2b)¹; however, use during STEMI has been associated with stent thrombosis.² Targeting an ACT with bivalirudin is not recommended; however, the ACT can be checked to make sure the drug has been delivered and is producing its intended effect. LMWH is rarely used; however, it can be considered among patients treated with upstream enoxaparin (class of recommendation 2b).¹

Antiplatelet agents include oral P₂Y₁₂ inhibitors and intravenous (IV) glycoprotein (GP) IIb/IIIa inhibitors. Cangrelor is an IV reversible P₂Y₁₂ inhibitor that has an emerging role in PCI and will be discussed separately. For stable ischemic heart disease, clopidogrel is the recommended P₂Y₁₂ inhibitor (class of recommendation 1).¹ For ad hoc PCI, this medication is given as a loading dose of 600 mg as soon as it is practical to do so. For planned PCI, clopidogrel can be given as a 300-mg loading dose or 75 mg/day if there is sufficient time for complete antiplatelet effect. Clopidogrel can usually be given to the patient on the catheterization laboratory table; however, based on patient circumstances, it might be deferred until immediately after PCI.

For ACSs, prasugrel or ticagrelor is preferred over clopidogrel and should be given as a loading dose as soon as it is practical to do so (class of recommendation 2a).¹ Prasugrel is given as a dose of 60 mg. Prasugrel is deferred until the coronary anatomy has been defined for NSTEMI. This medication is contraindicated among patients with previous intracranial hemorrhage, prior stroke, or transient ischemic attack and should be used with caution at a lower dose among patients 75 years of age or older or weighing less than 60 kg.¹ In the TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction), 73% of participants received study medication during PCI, defined as after the coronary guidewire was placed or within 1 hour of leaving the catheterization laboratory.³ Is there benefit to giving a P₂Y₁₂ inhibitor upstream of cardiac catheterization? The ACCOAST (Comparison of Prasugrel at the Time of

Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction) trial enrolled 4033 participants with NSTEMI and randomized them to prasugrel 30 mg before angiography versus placebo.⁴ The primary outcome of cardiovascular death, myocardial infarction (MI), stroke, urgent revascularization, or GP IIb/IIIa inhibitor bailout at 7 days was similar between treatment groups. However, TIMI (Thrombolysis in Myocardial Infarction) major bleeding and life-threatening bleeding unrelated to coronary artery bypass grafting (CABG) were increased by a factor of 3 and 6, respectively, for prasugrel versus placebo. Ticagrelor is given as a dose of 180 mg. The ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) trial enrolled 1862 participants with STEMI and randomized them to ticagrelor loading in the ambulance versus ticagrelor loading in the catheterization laboratory.⁵ Preloading did not improve ST-segment resolution or TIMI flow 3 at the time of initial angiography.

Cangrelor is an IV P₂Y₁₂ inhibitor that has been shown to reduce the risk of periprocedural MI, repeat coronary revascularization, or stent thrombosis among patients who had not been treated with an oral P₂Y₁₂ inhibitor or a GP IIb/IIIa inhibitor. Accordingly, this agent can be considered during PCI with a class of recommendation 2b.^{1,6} Cangrelor results in greater than 98% maximum platelet inhibition. It has rapid onset within 2 minutes and offset within 1 hour of discontinuation. After cangrelor infusion is discontinued, an oral P₂Y₁₂ inhibitor needs to be given as a loading dose. Special circumstances to consider using cangrelor include fentanyl and/or morphine co-administration, known or potential need for surgery after PCI, and inability to administer or retain oral medications.

The use of GP IIb/IIIa inhibitors (i.e., tirofiban, eptifibatide, abciximab) has evolved considerably since their introduction. These agents are no longer recommended for routine use in stable coronary artery disease (class of recommendation 3).¹ In ACSs, GP IIb/IIIa inhibitors have been studied upstream of cardiac catheterization (i.e., facilitated strategy) with the aim of improving preprocedure coronary flow, reducing infarct size, and improving survival. Dong et al.⁷ performed a meta-analysis on nearly 3000 patients with STEMI who received upstream eptifibatide or tirofiban versus in-laboratory eptifibatide or tirofiban. Upstream GP IIb/IIIa inhibitor use was associated with improved preprocedure coronary flow; however, it did not reduce recurrent MI or improve survival. GP IIb/IIIa inhibitors can also be administered intracoronary rather than intravenously; however, randomized trial data failed to find a benefit in regard to survival or recurrent MI from this approach.⁸ The FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial randomized nearly 2500 patients who presented within 6 hours of STEMI to upstream abciximab versus upstream abciximab with half-dose reteplase versus upstream placebo with abciximab immediately before PCI.⁹ Efficacy was similar between all treatment arms; however, major bleeding was increased from a facilitated approach, especially with thrombolytic therapy. Eitel et al.¹⁰ also conducted a meta-analysis to examine the association between facilitated PCI and mortality.

No benefit was observed from GP IIb/IIIa inhibitor-facilitated PCI, thrombolytic-facilitated PCI, or combination GP IIb/IIIa inhibitor/half-dose thrombolytic-facilitated PCI. In summary, facilitated (upstream) PCI with GP IIb/IIIa inhibitors or thrombolytic agents during STEMI is not recommended. Considerations for intraprocedural GP IIb/IIIa inhibitor use in ACS include large thrombus burden, no reflow, or slow flow (class of recommendation 2a).¹

THROMBUS IN VARIOUS CLINICAL SCENARIOS

Thrombus From de Novo Plaque Rupture

Plaque rupture or plaque erosion is the pathophysiologic event responsible for NSTEMI and STEMI. Thrombus is often believed to be universally present during ACSs; however, a closer look at thrombus grading finds that this is often not the case. Sianos and colleagues¹¹ examined more than 800 patients with STEMI. Almost 60% of individuals were found to have an occluded artery on initial angiography. One might assume that all occluded arteries were associated with large thrombus burden; however, the investigators reexamined thrombus grade after establishing some reperfusion from crossing the lesion with a guidewire or dilating a 1.5-mm balloon at the site of occlusion. After this strategy, nearly all cases could be reclassified into a different and often a smaller thrombus grade (Table 14.1). In 53.4%, there was no thrombus, possible thrombus, or small thrombus. Only in 28.2% was large thrombus burden detected. Large thrombus burden compared with small thrombus burden was an independent predictor for 2-year stent thrombosis (8.2% vs 1.3%; $P < .001$) and 2-year mortality (12.9% vs 9.4%; $P = .023$). In summary, when systematically evaluated for, large thrombus burden during STEMI is relatively infrequent and supports the current recommendation that routine use of aspiration thrombectomy during STEMI is not useful (class of recommendation 3).¹

TABLE 14.1 Thrombus Grading After Minimal Intervention^a

THROMBUS GRADE	DEFINITION	PROPORTION WITH GRADE (%)
G0	No thrombus; no angiographic characteristics of thrombus	7.9
G1	Possible thrombus; reduced contrast density, haziness, irregular lesion contour, or a smooth convex meniscus at the site of occlusion	19.4
G2	Definite thrombus; dimension $\leq 1/2$ of the vessel diameter	26.1
G3	Definite thrombus; dimension $> 1/2$ but < 2 vessel diameters	17.7
G4	Definite thrombus; dimension > 2 vessel diameters	28.2
G5	Unable to assess thrombus; vessel remains totally occluded	0.3

^aThrombus classification was performed after reperfusion from minimal intervention. Reperfusion was achieved after passage of the coronary guidewire or inflation of a small balloon (1.5 mm) at the site of occlusion.

Coronary Embolism

It is estimated that 3% of cases of ACS are caused by coronary embolism.¹² Although this is rare, it is important to consider coronary embolism because immediate and long-term management may be different than coronary plaque rupture events. Coronary embolism may originate from the left atrial appendage in the setting of atrial fibrillation, from the left ventricle in the setting of an apical aneurysm, from aortic valve or mitral valve disease (also endocarditis), from the venous circulation in the setting of a patent foramen ovale, or iatrogenic from a cardiovascular procedure (i.e., coronary and valvular interventions).

Characteristics that may help to distinguish coronary embolism from coronary thrombosis include large thrombus burden, thrombus in multiple coronary arteries, otherwise normal coronary arteries, and atrial fibrillation. Intravascular imaging may be helpful to rule out the presence of underlying coronary artery disease.

Long-term management should try to ascertain the cause of the coronary embolism and to prevent future events. This might necessitate anticoagulation in the setting of atrial fibrillation or valve thrombosis. Transesophageal echocardiography may be considered to evaluate for a patent foramen ovale.

Stent Thrombosis

An important cause of acute MI is stent thrombosis.¹³ In fact, in a relatively large registry, the proportion of STEMI cases caused by stent thrombosis increased from 6% in 2003 to 2004 to approximately 11% in 2009 to 2010.¹⁴ This is important because primary PCI for stent thrombosis is less effective (76%–80% successful reperfusion) than primary PCI for native artery occlusion.^{15,16} STEMI caused by stent thrombosis is also associated with an increased risk for long-term MI (~23%) and repeat stent thrombosis (~15%) compared with STEMI caused by native artery occlusion.¹⁴

Intravascular imaging can be helpful with the diagnosis of stent thrombosis. Optical coherence tomography is more sensitive than intravascular imaging in detecting thrombus.¹⁷ With current-generation drug-eluting stents (everolimus and zotarolimus-eluting), late and very late stent thrombosis is exceedingly rare; however, these complications are still seen during periods of inadequate antiplatelet therapy. Inadequate antiplatelet therapy might be the result of poor patient compliance but is also seen among patients undergoing noncardiac surgical procedures who have minimized or stopped their antiplatelet therapy.

Bypass Graft Thrombosis

Saphenous vein bypass graft thrombosis is common and often clinically silent. With routine imaging 6 months after CABG, 20.1% of patients have been found to have an occluded saphenous vein bypass graft, 2.5% with a high-grade stenosis, and 77.3% with widely patent conduits.¹⁸ Target vessel size smaller than 1.5 mm and female gender have been associated with predictors for graft failure. Saphenous vein bypass graft thrombosis presenting as an

ACS is often associated with large thrombus burden and high likelihood for no reflow with reperfusion. In such a patient, mechanical aspiration might be needed to effectively remove thrombus and restore bypass graft and coronary artery flow.

DEVICES TO REMOVE THROMBUS

Simple Aspiration Thrombectomy

Thrombus removal is an important tool; however, it can result in microembolization, which is evident by persistent ST-segment elevation or poor myocardial blush despite successful reperfusion of the epicardial coronary artery. Impaired myocardial perfusion is associated with long-term mortality rate of 23% to 29% compared with 3% to 4% among patients with normal myocardial perfusion.¹⁹ Thrombus removal can also result in acute ischemic stroke or systemic embolization.

The simplest way to retrieve coronary thrombus is with the use of a manual aspiration thrombectomy catheter. A variety of catheters are commercially available (Figure 14.1; see Table 14.1). The catheter is attached to a stopcock and syringe that is prepped with negative pressure and advanced over a 0.014-inch wire proximal to the site of occlusion. When the stopcock is turned to the open position, the catheter aspirates blood and thrombotic debris from the catheter tip into the syringe. The catheter is slowly advanced through the site of occlusion and externalized when the syringe is nearly filled with blood. Normally, one to two or more passes with the aspiration catheter are performed to restore epicardial blood flow. One can continue with more passes as needed until there is no more debris noted in the aspirate when run through a mesh filter or gauze. Many catheters now come preloaded with a stylet that can facilitate deliverability of the device to the site of occlusion. There is no clear advantage of one device over another. Table 14.2 provides pearls to consider for optimal use.

The TOTAL trial (Trial of Routine Aspiration Thrombectomy with PCI versus PCI alone in Patients with STEMI) trial enrolled more than 10,000 participants with STEMI to aspiration thrombectomy before PCI versus PCI alone.²⁰ Routine aspiration thrombectomy compared with PCI alone did not reduce the incidence of cardiovascular death, recurrent MI, cardiogenic shock, or heart failure within 180 days. Routine aspiration thrombectomy compared with PCI was associated with slight excess in strokes (0.7% vs 0.3%; $P = .02$). Based on these findings, treatment guidelines downgraded the routine use of aspiration thrombectomy to a class 3 recommendation.¹ Thus, although routine aspiration thrombectomy is no longer recommended, selective use based on clinical circumstances remains an important tool.

Mechanical Aspiration Thrombectomy

Alternatively, mechanical or active thrombectomy can be performed. One device is the AngioJet (Bayer Healthcare) (Table 14.3 and Figure 14.2). This is often referred to as rheolytic thrombectomy. This device shares many similarities with aspiration thrombectomy. AngioJet catheters



FIGURE 14.1 Commercially available aspiration thrombectomy catheters.

TABLE 14.2 Commercially Available Aspiration Thrombectomy Catheters

MANUFACTURER	DEVICE	SPECIAL FEATURES	PRELOADED WITH STYLET	GUIDE CATHETER (Fr)
Medtronic	Export AP		No	6, 7
	Export Advance		Yes	6, 7
Terumo	PriorityOne		Yes	6, 7
Teleflex	Pronto V3	Tapered distal tip, designed to prevent vessel damage	No	6
	Pronto V4 ^a	Tapered distal tip, designed to prevent vessel damage	No	5.5, 6, 7, 8
	Pronto LP ^b	Tapered distal tip, designed to prevent vessel damage	Yes	5, 6
Atrium Medical and Kaneka Corporation	Xpress-Way		Yes	6
Philips	QuickCat		No	6
Boston Scientific	Fetch 2		No	6

^aThe Pronto V4 has an embedded longitudinal wire for additional deliverability and kink resistance.

^bThe Pronto LP is intended for small vessels (~1.5 mm).

TABLE 14.3 Pearls for Optimal Use of Aspiration Thrombectomy Catheters

PEARL	REASON OR EXPLANATION
Make sure the guide catheter is fully engaged in the coronary artery.	Prevent systemic embolism of thrombus
Activate suction proximal to the lesion.	Prevent systemic embolism of thrombus
Keep suction activated until the device is completely removed from the body.	Firm thrombus can get trapped at the catheter tip, and prematurely stopping suction could liberate thrombus into the guide catheter and result in embolism.
After the device is removed from the body, back bleed from the hemostatic valve.	This can discharge retained thrombus as above.
Use caution opening the hemostatic valve if the guide catheter pressure is severely dampened.	Opening the hemostatic valve can entrain air into the guide catheter if there is pressure dampening (i.e., the tip of the guide catheter is making contact with the lesion or vessel wall).
Aspiration thrombectomy catheters can be used to infuse medications into the myocardial bed.	With poor coronary flow or forceful injection, intracoronary administration of medications through the guide catheter may end up in the systemic rather than coronary circulation.
The aspiration thrombectomy catheter can be difficult to advance to the target. In this scenario, consider a catheter that comes loaded with a stylet or select a low-profile device.	The stylet stiffens the catheter and enhances deliverability. Similarly, a guide extender may provide enough support to allow the thrombectomy catheter to track into position.
Despite being designed to be “kink resistant,” all catheters are relatively easy to kink.	Slow down during advancement of catheter into the body.



FIGURE 14.2 Commercially available rheolytic thrombectomy catheters.

require a 6-Fr guide catheter, except for the Spiroflex VG catheter, which is intended for saphenous vein graft (SVG) lesions in which a 7-Fr guide catheter is required. High-pressure saline jets are directed retrograde within the catheter (Figure 14.3). Saline escapes from proximal

outflow windows and returns to distal inflow windows while loosening thrombus in the process. This device might be relatively ineffective in removing organized thrombus. Rheolytic thrombectomy catheters create about 600 mm Hg at the catheter tip compared with about 10 mm Hg with aspiration thrombectomy catheters. There is potential for blood loss with this device, especially with multiple and prolonged runs; however, it is likely similar to the degree of blood loss with aspiration thrombectomy catheters. Some patients require a temporary pacemaker, especially when thrombectomy is performed in the right coronary artery. Some operators recommend theophylline infusion to prevent bradyarrhythmias.

The Penumbra device is an active suction device. The system consists of an engine to provide suction and the extraction catheter. The extraction catheters are similar to simple aspiration thrombectomy catheters (Table 14.4). The Penumbra device may be especially useful for large thrombus burden or inability to remove thrombus with aspiration thrombectomy catheters.

EXPERIMENTAL DEVICES

An alternative approach is to trap the thrombus within the coronary artery rather than retrieve it. This strategy was studied in the MASTER trial (Safety and Efficacy Study of the MGuard Stent After a Heart Attack).²¹ In this feasibility trial, a polyethylene terephthalate micronet mesh-covered

ANGIOJET® ULTRA THROMBECTOMY SYSTEM MECHANISM OF ACTION

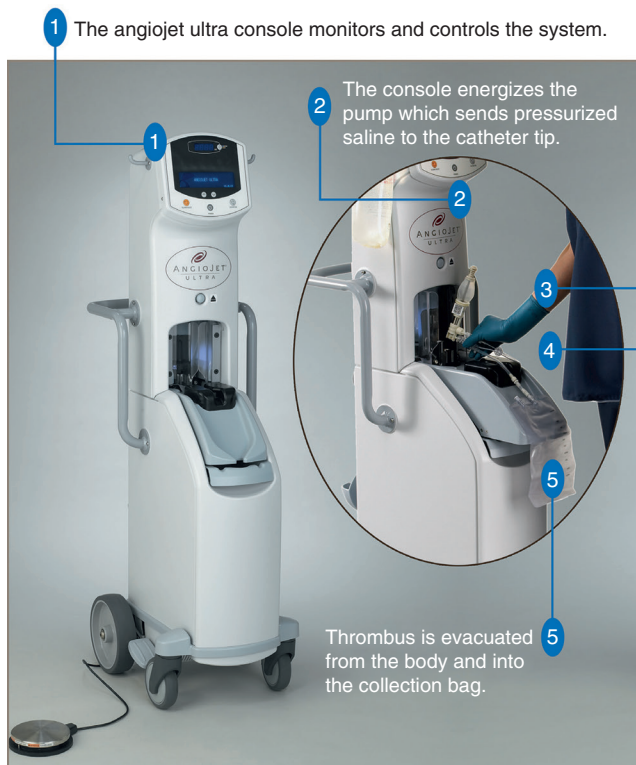


FIGURE 14.3 Schematic of mechanism of action of rheolytic thrombectomy. (Reprinted with permission from Bayer HealthCare LLC. The AngioJet is a registered trademark of Bayer.)

TABLE 14.4 Commercially Available Mechanical Thrombectomy Catheters

MANUFACTURER	DEVICE	RAPID EXCHANGE	GUIDE CATHETER (Fr)
Penumbra	Indigo System CAT RX: 1. Penumbra Engine 2. CAT RX	Yes	6
Bayer	AngioJet Distaflex ^a	No	6
	AngioJet Spiroflex	Yes	6
	AngioJet Spiroflex VG	Yes	7

^aThe AngioJet Distaflex is intended for small vessels (the tip is 4 Fr, and the body of the catheter is 5 Fr).

stent was compared with a commercially available bare-metal or drug-eluting stent during STEMI. The mesh-covered stent significantly improved postprocedure ST-segment resolution. Future studies will need to determine if this improves clinical outcomes.

As mentioned previously, intracoronary administration of a GP IIb/IIIa inhibitor does not appear to be beneficial compared with IV administration. Part of the reason for the lack of efficacy from this strategy could be attributable to impaired coronary flow, thus resulting in much of the drug being dispersed systemically. The ClearWay catheter (Atrium Medical) is a device that was designed to infuse drug (i.e., GP IIb/IIIa inhibitors) locally rather than intracoronary.²² This device is a 2.7-Fr rapid-exchange catheter that has a “weeping” polytetrafluoroethylene balloon that allows for local drug delivery.

DEVICES THAT ARE NOT BENEFICIAL

Embolic protection devices (i.e., a distal filter) are commonly used during revascularization of SVG lesions. The devices have been studied in native coronary artery occlusion; however, they are not used today because of a lack of efficacy.²³ Other devices that have been studied to some extent are the excimer laser and ultrasonic thrombectomy.^{24,25}

CASE

Figure 14.3 and Videos 14.1 to 14.5 highlight the clinical application of aspiration thrombectomy and rheolytic thrombectomy devices within the same patient during an acute MI. The patient was an 83-year-old man with prior CABG and PCI who presented to the hospital with an acute MI. He was taken for cardiac catheterization, and coronary angiography revealed an occluded SVG to the ramus intermedius that was presumed to be the culprit artery (see Figure 14.4 and Video 14.1). The site of occlusion was proximal to a previously placed stent. Aspiration thrombectomy was performed with an Export device; however, this only restored partial coronary flow (Figure 14.5; see Videos 14.2 and 14.3). Next, rheolytic thrombectomy was performed with the AngioJet Spiroflex device (see Video 14.4). Temporary pacing was not required. This was

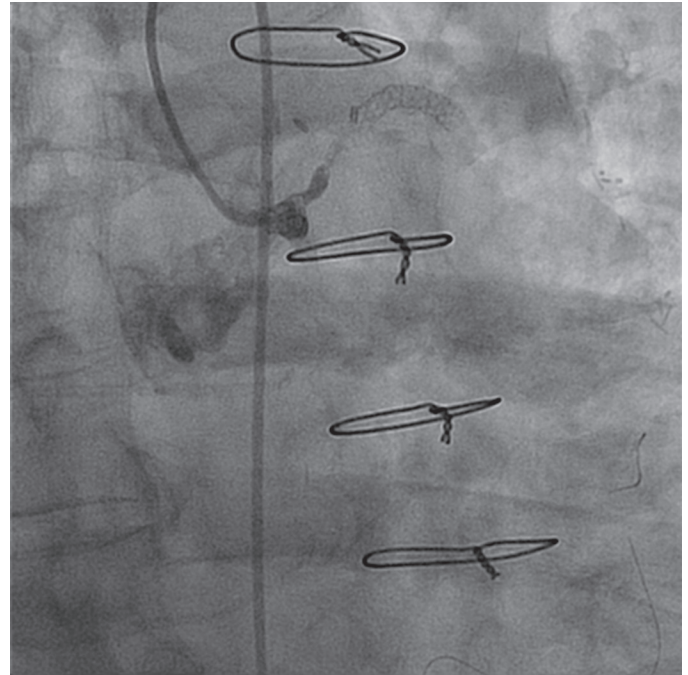


FIGURE 14.4 Saphenous vein graft occlusion. The site of occlusion is proximal to the previously placed stent.

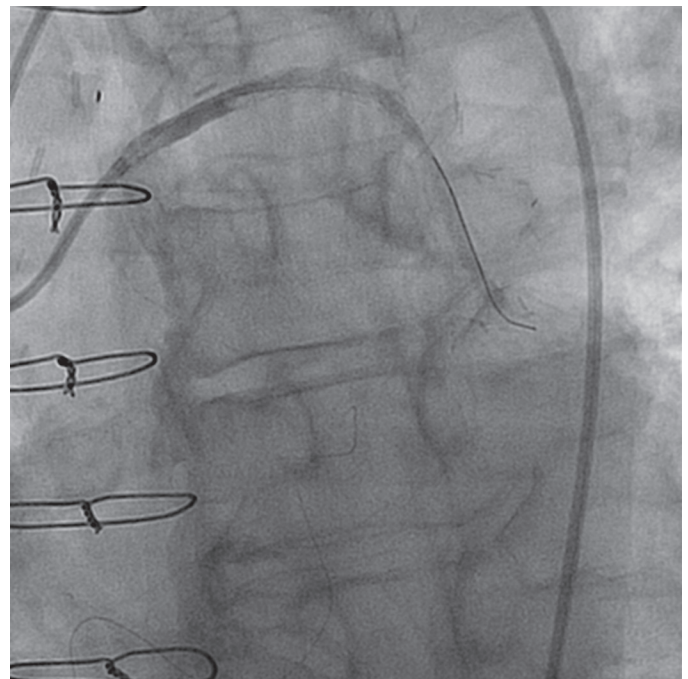


FIGURE 14.5 Improved but still poor flow after aspiration thrombectomy.

successful in restoring normal coronary flow (Figure 14.6; see Video 14.5).

CONCLUSIONS

In summary, thrombus is an important topic within interventional cardiology. Pharmacologic therapy and good interventional cardiology techniques are important to

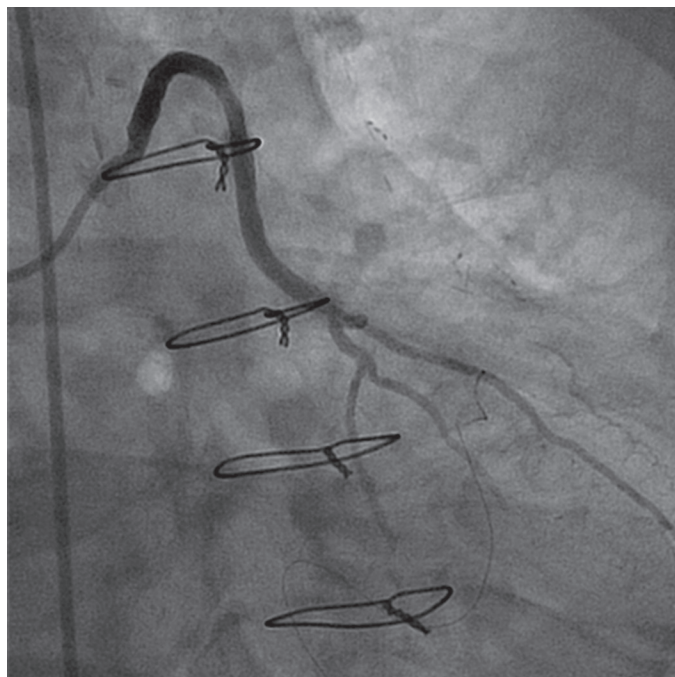


FIGURE 14.6 Successful reperfusion after rheolytic thrombectomy with the AngioJet Spiroflex device.

prevent thrombus formation during revascularization of stable and unstable coronary artery disease patients. Management of formed thrombus requires a critical appraisal to ascertain the size of the thrombus because many occluded vessels in patients with STEMI are actually associated with small thrombus burden. Simple aspiration thrombectomy and perhaps mechanical aspiration thrombectomy are important in select cases when there is large thrombus burden or when conventional management fails to improve coronary flow.

REFERENCES

1. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e18-e114.
2. Bavry AA, Elgendy IY, Mahmoud A, Jadhav MP, Huo T. Critical appraisal of bivalirudin versus heparin for percutaneous coronary intervention: a meta-analysis of randomized trials. *PLoS One*. 2015;10(5):e0127832.
3. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015.
4. Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med*. 2013;369(11):999-1010.
5. Montalescot G, van 't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med*. 2014;371(11):1016-1027.
6. Stone GW, Généreux P, Harrington RA, et al. Impact of lesion complexity on peri-procedural adverse events and the benefit of potent intravenous platelet adenosine diphosphate receptor inhibition after percutaneous coronary intervention: core laboratory analysis from 10854 patients from the CHAMPION PHOENIX trial. *Eur Heart J*. 2018;39(46):4112-4121.
7. Dong L, Zhang F, Shu X. Upstream vs deferred administration of small-molecule glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: insights from randomized clinical trials. *Circ J*. 2010;74(8):1617-1624.
8. Thiele H, Wöhrle J, Hambrecht R, et al. Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. *Lancet*. 2012;379(9819):923-931.
9. Ellis SG, Tendera M, de Belder MA, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med*. 2008;358(21):2205-2217.
10. Eitel I, Franke A, Schuler G, Thiele H. ST-segment resolution and prognosis after facilitated versus primary percutaneous coronary intervention in acute myocardial infarction: a meta-analysis. *Clin Res Cardiol*. 2010;99(1):1-11.
11. Sianos G, Papafakis MI, Daemen J, et al. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. *J Am Coll Cardiol*. 2007;50(7):573-583.
12. Raphael CE, Heit JA, Reeder GS, et al. Coronary embolus: an underappreciated cause of acute coronary syndromes. *JACC Cardiovasc Interv*. 2018;11(2):172-180.
13. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med*. 2006;119(12):1056-1061.
14. Brodie BR, Hansen C, Garberich RF, et al. ST-segment elevation myocardial infarction resulting from stent thrombosis: an enlarging subgroup of high-risk patients. *J Am Coll Cardiol*. 2012;60(19):1989-1991.
15. Chechi T, Vecchio S, Vittori G, et al. ST-segment elevation myocardial infarction due to early and late stent thrombosis: a new group of high-risk patients. *J Am Coll Cardiol*. 2008;51(25):2396-2402.
16. Ergelen M, Gorgulu S, Uyarel H, et al. The outcome of primary percutaneous coronary intervention for stent thrombosis causing ST-elevation myocardial infarction. *Am Heart J*. 2010;159(4):672-676.
17. Alfonso F, Dutary J, Paulo M, et al. Combined use of optical coherence tomography and intravascular ultrasound imaging in patients undergoing coronary interventions for stent thrombosis. *Heart*. 2012;98(16):1213-1220.
18. McLean RC, Nazarian SM, Gluckman TJ, et al. Relative importance of patient, procedural and anatomic risk factors for early vein graft thrombosis after coronary artery bypass graft surgery. *J Cardiovasc Surg (Torino)*. 2011;52(6):877-885.
19. Stone GW, Peterson MA, Lansky AJ, Dangas G, Mehran R, Leon MB. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. *J Am Coll Cardiol*. 2002;39(4):591-597.
20. Jolly SS, Cairns JA, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med*. 2015;372(15):1389-1398.
21. Stone GW, Abizaid A, Silber S, et al. Prospective, Randomized, Multicenter Evaluation of a Polyethylene Terephthalate Micronet Mesh-Covered Stent (MGuard) in ST-Segment Elevation Myocardial Infarction: the MASTER trial. *J Am Coll Cardiol*. 2012;60(19):1975-1984.
22. Stone GW, Maehara A, Witzensbichler B, et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA*. 2012;307(17):1817-1826.
23. Bavry AA, Kumbhani DJ, Bhatt DL. Role of adjunctive thrombectomy and embolic protection devices in acute myocardial infarction: a comprehensive meta-analysis of randomized trials. *Eur Heart J*. 2008;29(24):2989-3001.
24. Topaz O, Ebersole D, Das T, et al. Excimer laser angioplasty in acute myocardial infarction (the CARMEL multicenter trial). *Am J Cardiol*. 2004;93(6):694-701.
25. Brosh D, Bartorelli AL, Cribier A, et al. Percutaneous transluminal therapeutic ultrasound for high-risk thrombus-containing lesions in native coronary arteries. *Catheter Cardiovasc Interv*. 2002;55(1):43-49.



15

Fractional Flow Reserve And Nonhyperemic Pressure Ratios

MORTON J. KERN

RATIONALE FOR TRANSLESIONAL
PHYSIOLOGIC MEASUREMENTS, 263

DERIVATION OF FRACTIONAL FLOW
RESERVE AND NONHYPEREMIC PRESSURE
INDICES, 263

ROLE OF SUBMAXIMAL CORONARY
HYPEREMIA WITH CONTRAST
FRACTIONAL FLOW RESERVE, 265

NONHYPEREMIC PRESSURE RATIOS, 267

CORONARY FLOW RESERVE VERSUS
FRACTIONAL FLOW RESERVE, 268

FRACTIONAL FLOW RESERVE AND
MYOCARDIAL BED SIZE, 270

TECHNIQUE OF INTRACORONARY
PRESSURE MEASUREMENT, 270

PHARMACOLOGIC CORONARY
HYPEREMIA, 271

VALIDATION OF FRACTIONAL FLOW
RESERVE AND NONHYPEREMIC PRESSURE
RATIO, 271

DISCORDANCE BETWEEN
NONHYPEREMIC PRESSURE RATIO AND
HYPEREMIC INDICES, 272

FRACTIONAL FLOW RESERVE/
NONHYPEREMIC PRESSURE RATIO FOR
SPECIFIC ANGIOGRAPHIC SUBSETS, 272

MULTIVESSEL DISEASE PERCUTANEOUS
CORONARY INTERVENTION, 274

NONHYPEREMIC PRESSURE RATIO AND
INTERMEDIATE LESION ASSESSMENT, 275

LEFT MAIN STENOSIS, 276

SERIAL (MULTIPLE) LESIONS AND DIFFUSE
CORONARY ARTERY DISEASE, 278

DIFFUSE CORONARY DISEASE, 278

FRACTIONAL FLOW RESERVE IN ACUTE
CORONARY SYNDROME, 280

POST-PERCUTANEOUS CORONARY
INTERVENTION PHYSIOLOGY, 281

ASSESSING COLLATERAL FLOW, 283

INDEX OF MICROCIRCULATORY
RESISTANCE, 284

SUMMARY AND FUTURE
DIRECTIONS, 284

THE FUTURE OF INTRACORONARY
PHYSIOLOGY: ANGIOGRAPHICALLY
DERIVED FRACTIONAL FLOW
RESERVE, 287

Coronary blood flow and pressure measurements across a stenotic coronary artery describe the ischemic potential of a specific lesion. The use of translesional pressure measurements (i.e., fractional flow reserve [FFR] and non-hyperemic pressure ratios [NHPRs; e.g., instantaneous wave-free ratio [iFR], distal/aortic mean pressure ratio [P_d/P_a]]) have demonstrated improved percutaneous coronary intervention (PCI) outcomes compared with angiography alone. The integration of translesional pressure measurements as an adjunct to coronary angiography and PCI has made a significant impact on clinical decision making and patient outcomes. Translesional pressure measurements are now recommended by national and international cardiac societal guidelines as part of the standard of care for coronary revascularization. This chapter reviews the theory and applications of FFR and NHPRs for clinical practice.

RATIONALE FOR TRANSLESIONAL PHYSIOLOGIC MEASUREMENTS

The rationale for using translesional coronary physiologic assessment arises from two tenets: (1) that the coronary angiogram has significant limitations to demonstrating the clinical significance of lesions accurately and (2) that decisions for revascularization by either PCI or coronary artery bypass grafting (CABG) should be based on the presence of ischemia, evidence of which may not

be available based on the angiogram or from noninvasive testing.¹⁻³

Coronary angiography produces a two-dimensional silhouette image of the three-dimensional (3D) vascular lumen. The interpretation of this image is often unreliable as evidenced from the poor correlation between ischemia testing with angiographic percent diameter stenosis, particularly for intermediately narrowed (between 30% and 80% diameter stenosis) lesions. Moreover, angiography cannot provide morphologic details contributing to vascular resistance and flow limitation, particularly for eccentric lesions (Figures 15.1 and 15.2). Other confounding artifacts of angiographic lesion interpretation include contrast streaming, branch overlap, vessel foreshortening, calcifications, and ostial origins, which all contribute to uncertainty. This uncertainty can be overcome with physiologic measurements of pressure and flow.

DERIVATION OF FRACTIONAL FLOW RESERVE AND NONHYPEREMIC PRESSURE INDICES

Because angiographic visualization of coronary detail was poor, in 1979, Dr. Andreas Gruentzig, the inventor of balloon angioplasty, incorporated a very small second lumen on his original balloon catheter to measure distal coronary pressure. Using the aortic guide catheter pressure to represent the normal desired endpoint of coronary pressure, success could be gauged by the elimination of the poststenotic

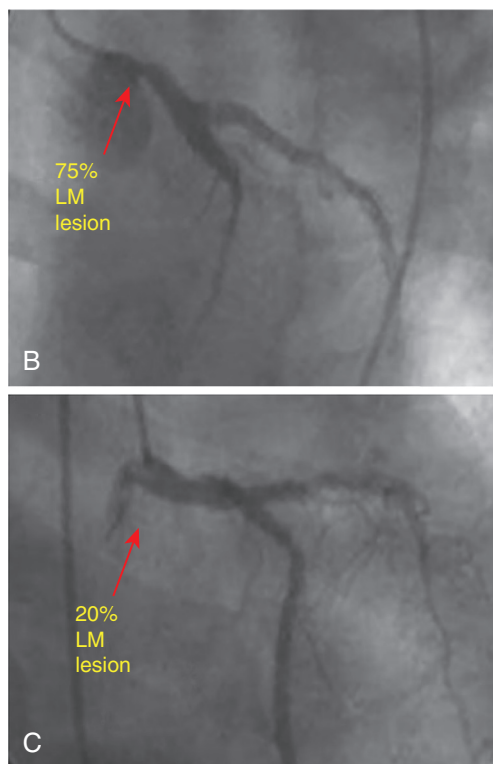
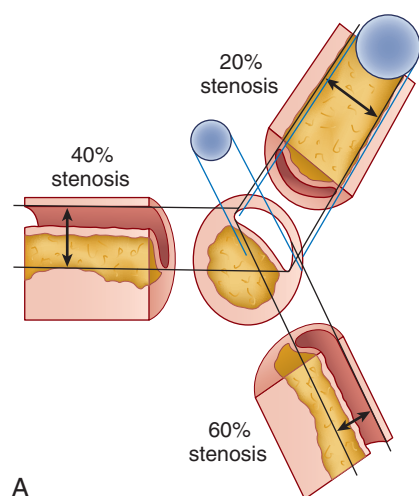


FIGURE 15.1 Rationale for the need for coronary physiologic lesion assessment. **A**, Estimate of any angiographic lumen requires multiple views but remains poorly related to determinants of pressure loss. Viewed from different radiographic projections, the eccentric lumen produces an image with a high degree of uncertainty related to true lumen size and its impact on coronary blood flow. The same lesion may appear significant in one radiographic view (**B**) and nonsignificant in another (**C**). *LM*, Left main.

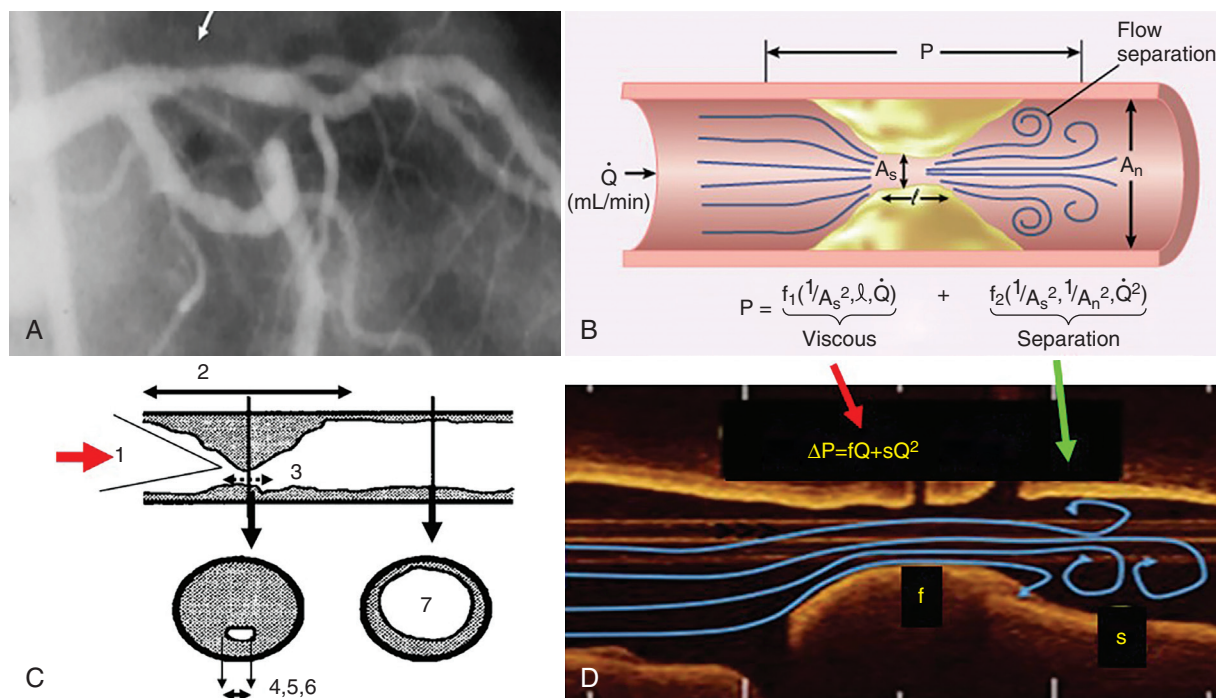


FIGURE 15.2 Determinants of pressure loss across a coronary stenosis. **A**, Angiogram with intermediate narrowing of the left anterior descending coronary artery. **B**, Diagram of components of change in pressure across the stenosis, including the viscous friction coefficient and the separation coefficient; each of these has factors related to area stenosis, length of stenosis, and area of normal reference vessel and separation coefficient. Flow is linearly related to viscous friction and related in exponential fashion to the separation coefficient. Most of the components of the viscous and separation coefficient are unknown anatomically. **C**, There are at least seven morphologic factors that produce pressure loss across a stenosis, most of which cannot be measured from the angiogram: (1) entrance angle, (2) length of disease, (3) length of lesion, type of lesion (4, eccentric, 5, concentric, 6, irregular), and (7) reference vessel size. **D**, An optical coherence tomography cross section showing the flow pattern of convergence and turbulence across the stenosis. The impact of the frictional coefficient occurs principally at the lesion, whereas separation coefficient results in energy loss principally in the poststenotic area.

pressure gradient ($\Delta P = P_d - P_a$, aortic pressure). To normalize for different aortic pressures, the P_d/P_a ratio was also computed. The use of pressure to guide the angioplasty procedure was not widely accepted because of technical limitations and limited supporting data. It was not until years later when Drs. Nico Pijls and Bernard De Bruyne developed and validated an index for determining the physiologic impact of coronary stenoses, called the FFR.^{4,6} FFR is the percent of normal flow through a stenotic artery and measured as the ratio of mean P_d/P_a during maximal hyperemia. In the catheterization laboratory, the coronary pressure beyond the stenosis is measured with a high-fidelity pressure transducer mounted 3.0 cm from the angioplasty guidewire. In normal coronary arteries, aortic pressure is transmitted completely without any pressure loss, that is, intracoronary (IC) pressure is normally equal to aortic pressure measured from the guide catheter.

Using the ratio of distal stenosis pressure to aortic pressure as a surrogate for the ratio of poststenotic flow to normal flow measured at constant and minimal myocardial resistances (i.e., maximal hyperemia), Pijls et al.⁵ derived the percentage of normal coronary blood flow expected to go through the stenotic artery (Figure 15.3). FFR also describes the separate flow contributions by the coronary artery, the myocardium, and the collateral supply. FFR of the coronary artery (FFR_{cor}) is defined as the maximum coronary artery flow in the presence of a stenosis divided by the theoretic normal maximum flow of the same artery (i.e., the maximum flow in that artery if no stenosis were present). Similarly, FFR of the myocardium (FFR_{myo}) is defined as maximum myocardial (artery and bed) flow distal

to an epicardial stenosis divided by its value if no epicardial stenosis were present. Note that at maximal hyperemia FFR_{cor} is about equal to FFR_{myo} because myocardial bed resistance is minimal. The difference between FFR_{myo} and FFR_{cor} is FFR of the collateral flow.

The following equations are used to calculate the FFR of a coronary artery and its dependent myocardium:

$$FFR_{cor} = (P_d - P_w) / (P_a - P_w)$$

$$FFR_{myo} = (P_d - P_v) / (P_a - P_v)$$

$$FFR_{collateral} = FFR_{myo} - FFR_{cor}$$

in which P_a , P_d , P_v , and P_w are pressures of the aorta, distal artery, venous (or right atrial [RA]), and coronary wedge (during balloon occlusion) pressures, respectively. Because FFR_{cor} uses P_w , it can be calculated only during coronary angioplasty.

Regarding the use P_v , in most clinical circumstances, P_v is negligible relative to aortic pressure and omitted from the calculations. Toth et al.⁷ measured the impact of RA pressure on the difference between the simplified FFR without using P_v and full-formula FFR_{myo} in 1675 stenoses from 1235 patients. For P_v of 10 mm Hg or less, an FFR greater than 0.80 was never recalculated to produce an FFR_{myo} less than 0.75. Even when P_v was 20 mm Hg or greater, only 4% of lesions had FFR_{myo} less than 0.75. However, in patients with P_v greater than 20 mm Hg and P_a less than 80 mm Hg, FFR differs significantly from FFR_{myo} . Thus, an RA pressure greater than 10 mm Hg may influence FFR by ± 0.02 units and more so in patients with both elevated RA pressure and reduced systemic pressure.

Fractional flow reserve reflects both antegrade and collateral (or bypass graft) myocardial perfusion rather than merely trans-stenotic pressure loss (i.e., a stenosis pressure gradient). Because it is calculated only at peak hyperemia and excludes the microcirculatory resistance from the computation, FFR, unlike the coronary velocity reserve, is largely independent of basal flow, heart rate, systemic blood pressure, or status of the microcirculation.

An FFR value less than 0.80 represents an ischemic lesion response and supports the decision to revascularize (PCI or CABG; see clinical applications). Figures 15.4 and 15.5 illustrate the application of FFR for coronary stent placement.

ROLE OF SUBMAXIMAL CORONARY HYPEREMIA WITH CONTRAST FRACTIONAL FLOW RESERVE

Contrast media can induce a hyperemic response of approximately 60% to 80% of that produced by adenosine with a duration of about 20 seconds. Contrast fractional flow reserve (cFFR) is easily performed in the same way as FFR using a 10-cc bolus of contrast and measuring P_d/P_a at the lowest value. A cFFR below 0.83 has a greater than 90% accuracy for FFR less than 0.80 and supports intervention or deferral of stenting. Johnson et al.⁸ found that cFFR had equivalent performance against FFR less than 0.8 (78.5% vs 79.9% accuracy; $P = .78$). Leone et al.⁹ compared cFFR, P_d/P_a ,

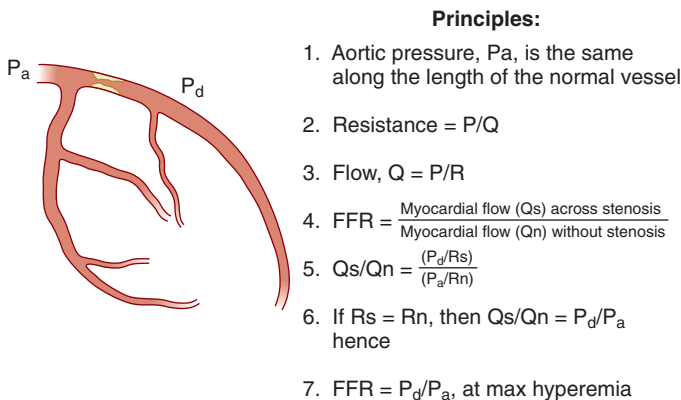


FIGURE 15.3 Simplified derivation of fractional flow reserve (FFR). FFR is the ratio of maximal myocardial perfusion in the stenotic territory divided by maximal hyperemic flow in the same region in the hypothetical case the lesion was not present. FFR represents the fraction of hyperemic flow that persists despite the presence of the stenosis. This ratio of two flows is calculated solely from the ratio of mean coronary pressure (P_d) divided by mean aortic pressure (P_a) provided both pressures are recorded under conditions of maximal hyperemia. Aortic pressure (P_a) is the same along the length of the normal vessel. FFR is defined as myocardial flow (Qs) across stenosis/myocardial flow (Qn) without stenosis. To derive FFR, assume resistance = P/Q , then flow, $Q = P/R$, and that $Qs/Qn = (P_d/Rs) / (P_a/Rn)$, in which Rs and Rn is resistance in the stenotic and normal bed, respectively, which are identical at maximal hyperemia. If $Rs = Rn$, then $Qs/Qn = P_d/P_a$, which is $FFR = Qs/Qn = P_d/P_a$. (Modified from Pijls NH, van Son JA, Kirkeeide RL, et al. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation*. 1993;87:1354-1367.)

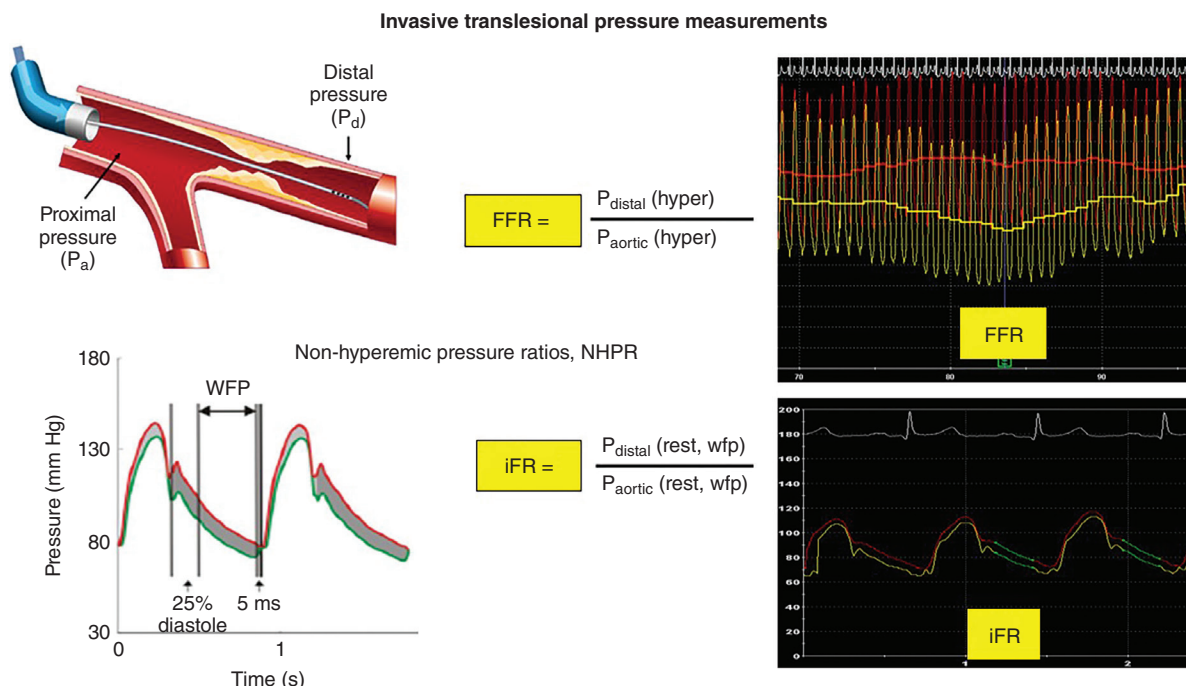


FIGURE 15.4 Invasive translesional pressure measurements. *Top*, diagram of a pressure wire across a stenosis with guide catheter in place at the coronary ostium. Formula for fractional flow reserve (FFR). FFR is P_{distal} (in which P is pressure) during hyperemia (hyper). The *upper right* tracing shows the FFR value taken at the lowest P_d/P_a during hyperemia. *Bottom panel*, graphic demonstrating the wave-free period of diastole (WFP) in which the instantaneous wave-free ratio (iFR) is computed. *Right lower panel*, a tracing of the iFR signal (green denotes the WFP used for the P_d/P_a ratio). (Data from Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol* 2012; 59:1392–402)

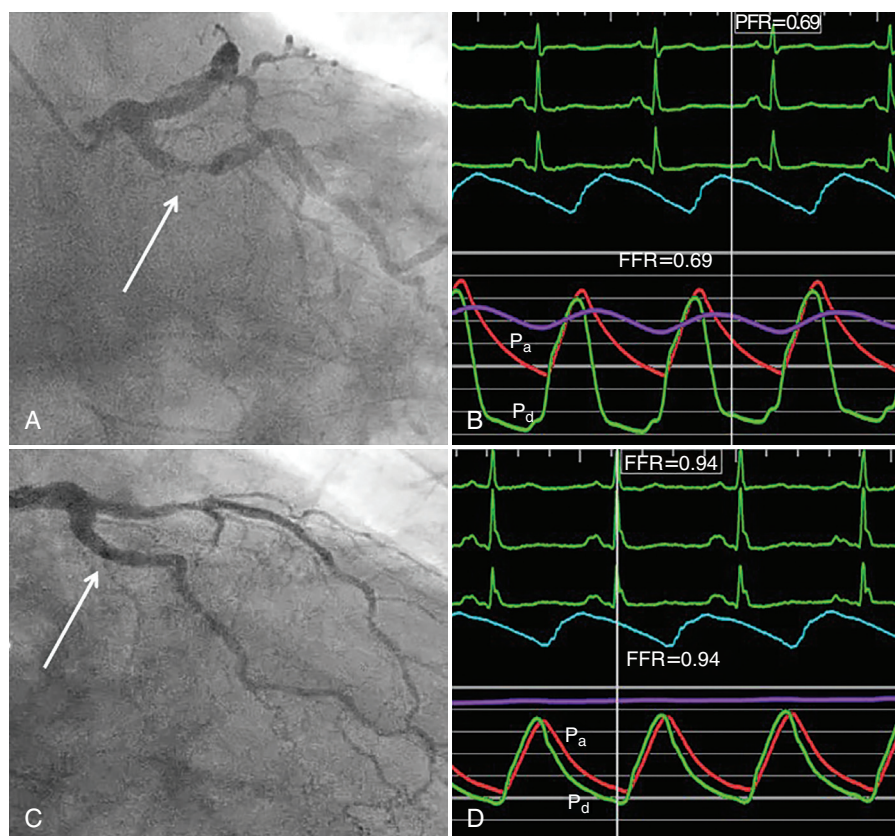


FIGURE 15.5 Case example of 72-year-old man with typical angina. Although fractional flow reserve (FFR) is not required, the percutaneous coronary intervention (PCI) of the circumflex stenosis (**A**, pre-stent, arrow) was performed with a 0.014-inch fiberoptic pressure wire to illustrate the significant initial gradient (**B**, FFR pre-stent, 0.69) and the resolution of any residual gradient after stenting (**C**, post-stent FFR, 0.94). Panel (**D**) shows post PCI pressure ratio. Note near matching of P_d and P_a with an FFR of 0.94 corresponding to widely patent CFX stent result. P_a , pressure, aortic; P_d , pressure, distal to stenosis.

and FFR and found a binary cutoff of 0.83 for cFFR was the best for prediction of FFR and more accurate than resting P_d/P_a (cutoff of 0.92) and iFR (cutoff of 0.90). To maximize the accuracy of cFFR, a hybrid approach has been proposed deferring revascularization when cFFR is greater than 0.88 and stenting when cFFR is 0.83 or less. Advantages of cFFR include universal availability with any FFR system, no additional expense, and minimal side effects related to those of contrast media. Because of the short half-life of contrast hyperemia, cFFR is not suitable for pressure pullback curves. For a borderline cFFR (~ 0.83), one should perform adenosine-FFR.

NONHYPEREMIC PRESSURE RATIOS

Adenosine-free or NHPRs were developed as alternatives to hyperemic pressure ratios (FFR, cFFR) and appear to be clinically noninferior to FFR in large multicenter trials. The first NHPR developed was the iFR, a resting translesional

pressure ratio taken during a specific diastolic interval in which the natural wave reflections in the cardiovascular system are quiescent. During this wave-free period, microvascular resistance is constant (but not minimal) and therefore meeting one condition of FFR without inducing hyperemia (i.e., need for adenosine)¹⁰ (Figure 15.6). All NHPRs use the ratio of distal coronary pressure and aortic pressure but differ in the portion of the diastolic period of the cardiac cycle that is measured. NHPRs are divided into diastolic subcycle (iFR, diastolic pressure ratio, diastolic hyperemia-free ratio) or whole-cycle indices (P_d/P_a , resting full-cycle ratio) (Figure 15.7). The reproducibility of NHPRs depends on a stable resting coronary blood flow. Measurements obtained shortly after saline flushing, contrast, or nitroglycerin (NTG) administration may be artifactually lowered because of residual hyperemia. Other factors, including drift, guide catheter dampening, and artifacts, affect both NHPR and FFR. Advantages and limitations of hyperemic and NHPRs in the catheterization laboratory are summarized in Table 15.1.

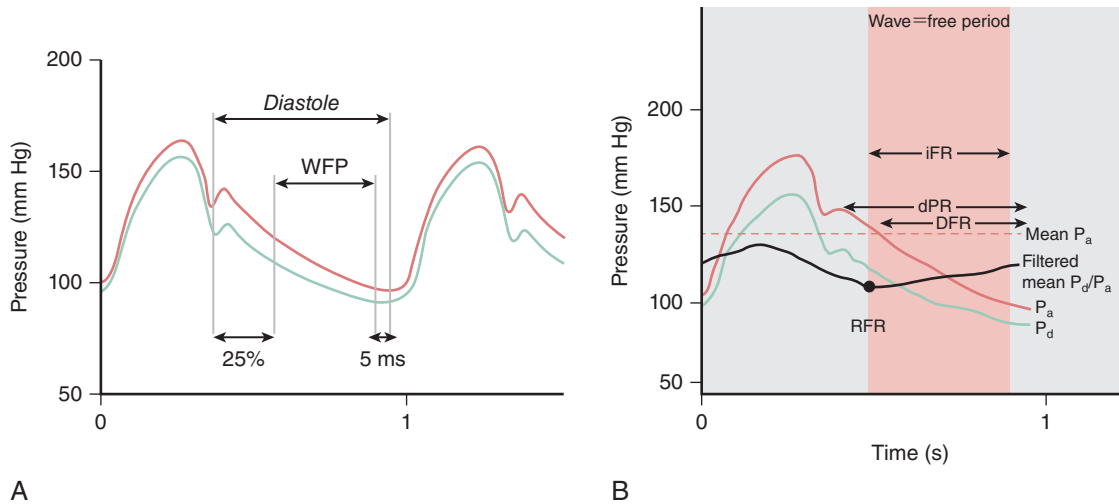


FIGURE 15.6 Calculations of nonhyperemic pressure ratios (NHPRs). **A**, The instantaneous wave-free ratio (iFR, Philips Medical) is defined as average distal/aortic mean pressure ratio (P_d/P_a) during the wave-free period (WFP). The WFP begins 25% of the way into diastole and ends 5 ms before the end of diastole. **B**, There are several other NHPRs. The diastolic pressure ratio (dPR, Opsens Inc.) is defined as average P_d/P_a during entire diastole. The diastolic hyperemia-free ratio (DFR, Boston Scientific) is defined as average P_d/P_a during the diastolic period when the P_a is less than mean P_a with a negative slope. The resting full-cycle ratio (RFR, Abbott Vascular) is defined as the lowest filtered mean P_d/P_a during the entire cardiac cycle. (Modified from Kogame N, Ono M, Kawashima H, et al. The impact of coronary physiology on contemporary clinical decision making. *J Am Coll Cardiol Interv.* 2020;13:1617-1638.)

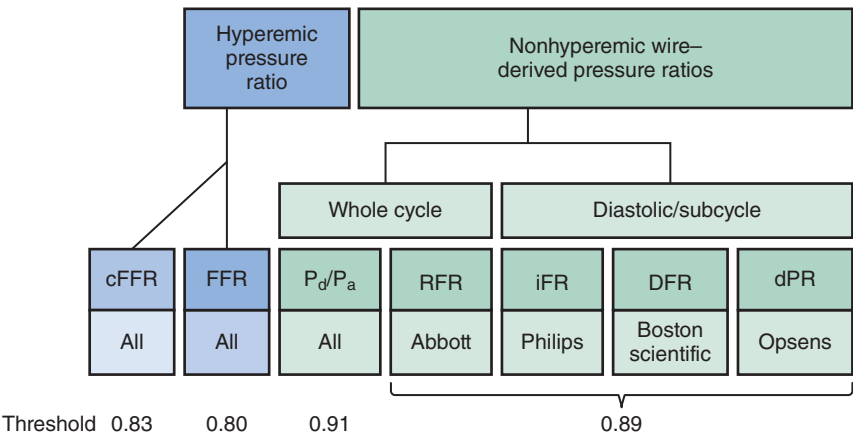


FIGURE 15.7 Translesional coronary hemodynamic indices. There are two hyperemic pressure ratios (using mean distal/aortic mean pressure ratio [P_d/P_a] at hyperemia), contrast fractional flow reserve (cFFR) (submaximal) and maximal fractional flow reserve (FFR), and five nonhyperemic pressure ratios, two whole-cycle (P_d/P_a generic and RFR by Abbott) and three diastolic subcycle (instantaneous wave-free ratio [iFR] by Philips, DFR by Boston Scientific, and dPR by Opsens). Ischemic threshold values are display beneath each index. (Modified from Kogame N, Ono M, Kawashima H, et al. The impact of coronary physiology on contemporary clinical decision making. *J Am Coll Cardiol Interv.* 2020;13:1617-1638.)

TABLE 15.1 Advantages and Limitations of Hyperemic and Nonhyperemic Pressure Ratios in the Catheterization Laboratory

	HYPEREMIC INDICES (FFR, cFFR)	NHPR (DIASTOLIC SUBCYCLE) iFR, DFR, dPR, RFR (WHOLE CYCLE)	NHPR: P_d/P_a (WHOLE CYCLE)
Ischemic threshold	0.80, 0.83	0.89	0.91
Validation	Stress ECG, echocardiography, nuclear testing	FFR, PET, CFR	FFR, PET, CFR
Pharmacologic hyperemia required	Yes	No	No
Flow variation	Adenosine related	Basal flow related	Less basal flow related
Proprietary software	No	Yes	No
Serial lesion "cross talk"	Yes	No	No
RCT data	Yes	Yes for iFR	No

cFFR, Contrast media FFR; CFR, coronary flow reserve; DFR, diastolic flow ratio (Acist Medical); dPR, diastolic pressure ratio (Opsens Inc.); ECG, electrocardiography; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio (Abbott Vascular); NHPR, nonhyperemic pressure ratio; P_d/P_a , distal/aortic mean pressure ratio; PET, positron emission tomography; RCT, randomized controlled trial; RFR, resting flow ratio (Boston Scientific).

CORONARY FLOW RESERVE VERSUS FRACTIONAL FLOW RESERVE

Coronary flow reserve (CFR) differs from FFR in several significant ways. CFR is defined as the ratio of peak hyperemic flow (or velocity) to basal flow (Figure 15.8). CFR is altered by changing maximal and basal flow velocity values, which vary with heart rate, blood pressure, and contractility. FFR does not depend on basal flow levels because it is computed only at maximal flow and is unaffected by changing hemodynamics or the status of the microcirculation. CFR greater than 2.0 represents a nonischemic value with an unknown normal value because CFR can

change depending on existing conditions of the patient. In contrast, FFR has an absolute normal value of 1.0 for every artery, every patient, and every condition. Whereas FFR is specific for determining the ischemic potential of a specific epicardial coronary stenosis, CFR provides the maximal flow across both the epicardial (R1) and microvascular (R2, R3) resistances. If either one or both is abnormal, CFR is abnormal, with no way to distinguish the contribution of the stenosis to impaired flow reserve (Figure 15.9). For these reasons, FFR is preferred over CFR for in-laboratory lesion assessment. Figure 15.10 illustrates the functions of the micro- and macrocirculations and invasive physiologic indices used in their assessment.¹¹

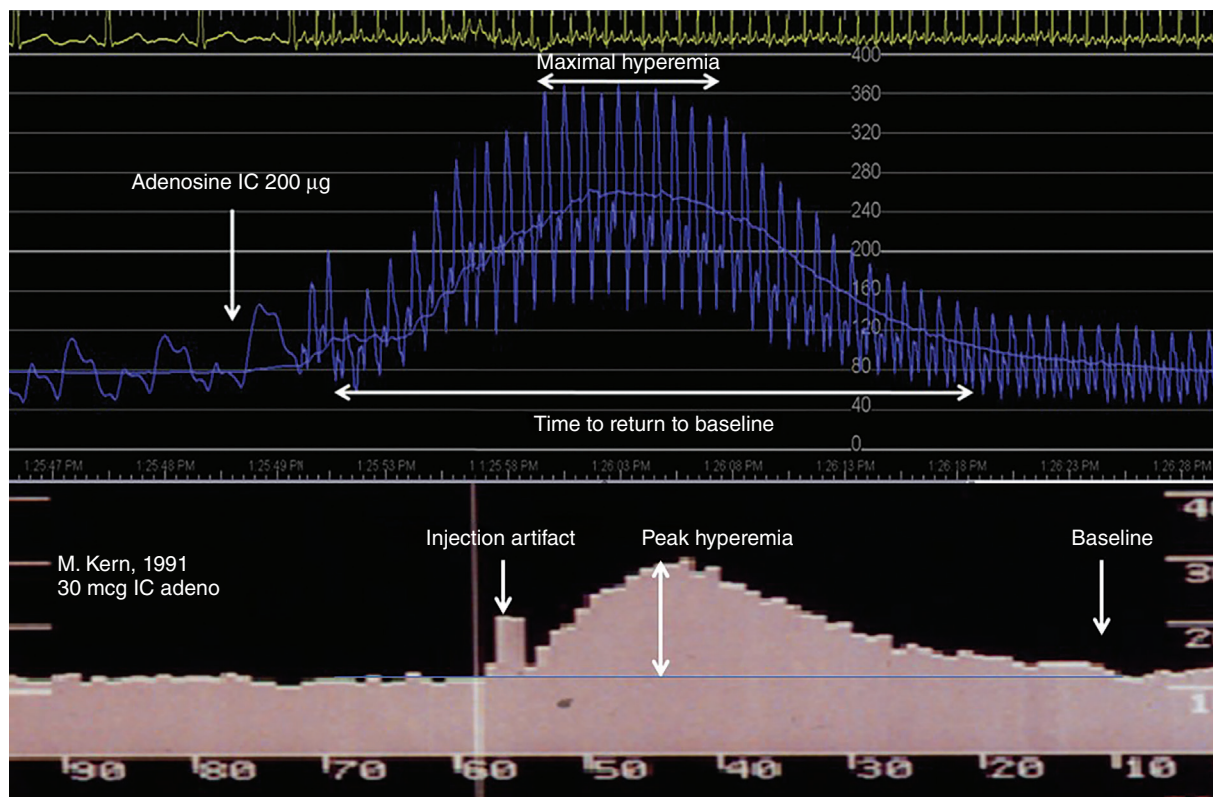


FIGURE 15.8 Intracoronary (IC) Doppler flow velocity with IC adenosine. *Top panel* depicts zero cross Doppler with the time course of hyperemia after a 30- μ g bolus of IC adenosine. The time course is about 30 to 45 seconds from injection (arrow) to return to baseline. *Lower panel*, spectral IC Doppler wire with adenosine bolus injection of 30 μ g. Time on the x-axis is marked in 10-second divisions. (*Bottom panel* from Kern M, 1991; *top panel* adapted from Adgej J, Toth GG, Johnson NP, et al. Intracoronary adenosine: dose-response relationship with hyperemia. *J Am Coll Cardiol Interv*. 2015;8(11):1422-1430.)

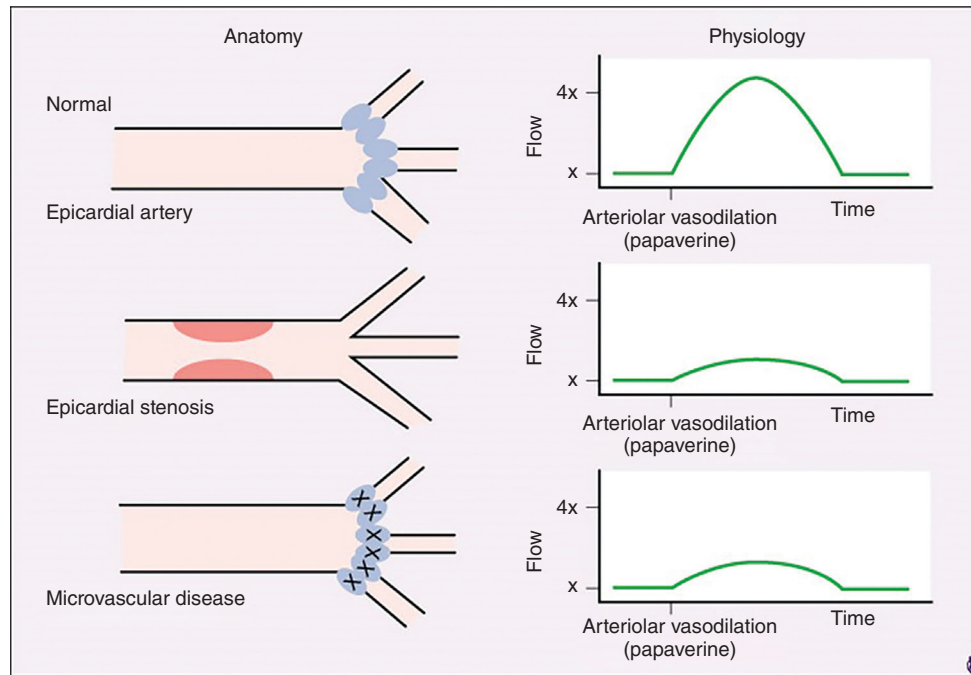


FIGURE 15.9 Two components of coronary artery resistance, the epicardial R1 and the microvascular R2 resistance, contribute to the generation of coronary flow reserve (CFR). When both components are normal (top panel), CFR is normal. *Middle panel*, if either epicardial resistance is present (i.e., a stenosis) or if there is microvascular disease (*lower panel*), CFR can be impaired. For this reason, CFR was not useful for epicardial lesion assessment. CFR measures sum of flow through epicardial and microvasculature. CFR cannot distinguish between a stenosis and an impaired microcirculation.

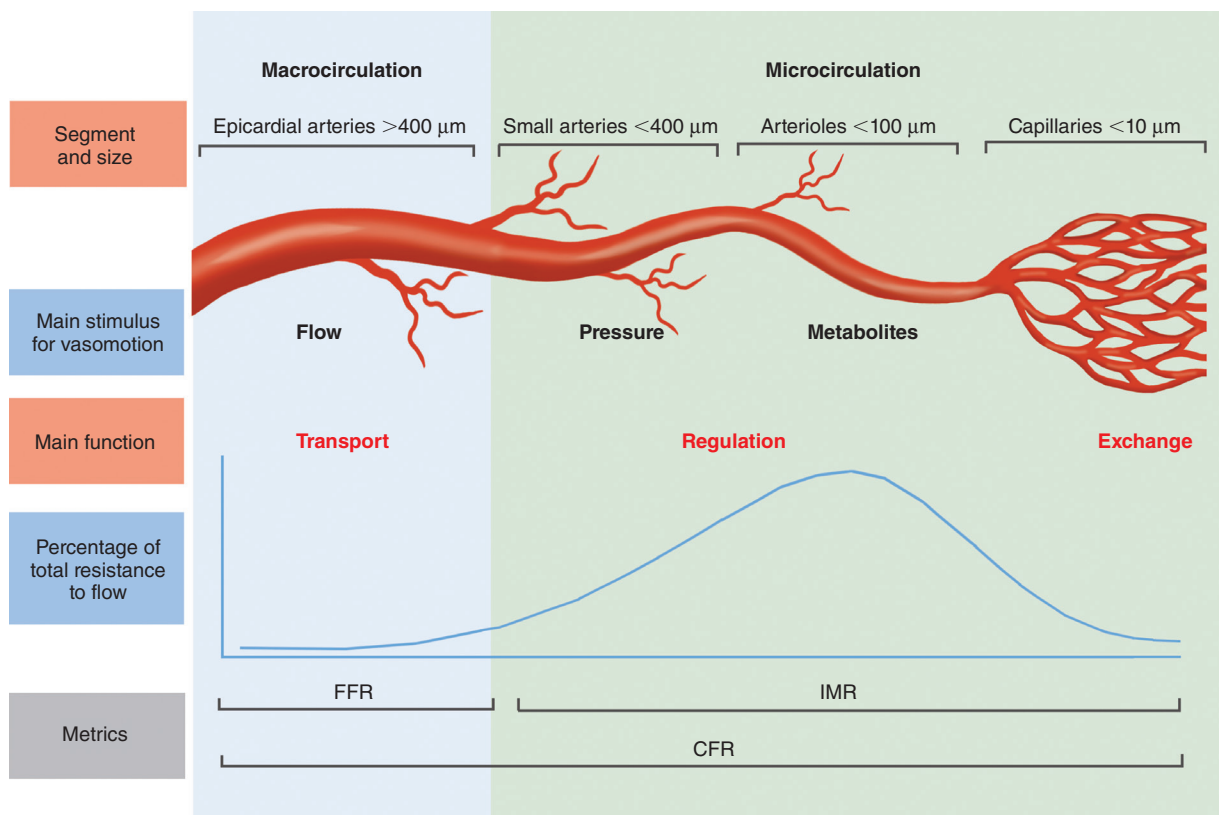


FIGURE 15.10 Micro- and macrovascular function in coronary artery disease. are depicted in this diagram of the components of each section. Macrovascular disease involves epicardial arteries larger than 400 μm . The microcirculation is divided into small arteries 400 to 100 μm , arterioles of approximately 100 μm , and capillaries smaller than 10 μm . Each size artery is responsible for a part of nutrient transport, flow regulation, and exchange of oxygen and nutrients to the myocardium. Flow resistance increases dramatically across the arterial circuit to the capillaries. The invasive physiologic metrics used to measure the functions include fractional flow reserve (FFR) and nonhyperemic pressure ratio (NHPR) for the macro circulatory responses and the index of microvascular resistance (IMR) and coronary flow reserve (CVR) spanning both the macro- and microcirculation. (From DeBruyne B, Oldroyd KG, Pijls NHJ. Microvascular (dys)function and clinical outcome in stable coronary disease. *J Am Coll Cardiol*. 2016;67(10):1170-1172.)

FRACTIONAL FLOW RESERVE AND MYOCARDIAL BED SIZE

An important concept to understanding the visual–functional mismatch of angiographic lesion severity and FFR is the relationship of myocardial bed size to epicardial flow. The larger the myocardial mass subtended by a vessel, the larger the hyperemic flow, and in turn, the larger the gradient and the lower the FFR for a given stenosis ([Figure 15.11](#)). This explains why a stenosis with a minimal cross-sectional area of 4 mm² has totally different hemodynamic significance in the proximal left anterior descending coronary artery (LAD) versus a more distal location or region such as might be supplied by a second marginal branch in the lateral wall distribution. Proof of this concept was demonstrated by Iqbal et al.,¹² whereby an intermediately stenotic LAD supplying the anterior and inferior myocardial beds in a patient with an occluded right coronary artery (RCA) had an FFR of 0.72. After stenting and opening the RCA, reducing the LAD myocardial bed, the FFR across the LAD now rose to 0.84. In a similar manner, the hemodynamic significance of a particular stenosis may change if the perfusion territory changes after myocardial infarction (MI). It is for this reason that FFR in patients with ST-elevation myocardial infarction (STEMI) may not be valid until the dynamic changes of the acute injury are over. Regardless of the visual appearance, FFR accounts for the flow through the epicardial artery related to the bed supplied.

TECHNIQUE OF INTRACORONARY PRESSURE MEASUREMENT

Fractional flow reserve/NHPR can be easily measured using a 5- or 6-Fr guide catheter and a sensor wire or microcatheter. After diagnostic angiography with a catheter seated in the coronary ostium, the steps to measure NHPR/FFR are as follows:

1. Anticoagulate with intravenous (IV) heparin (usually 70–100 U/kg or bivalirudin). IC nitroglycerin (100–200-μg bolus) is administered before guidewire insertion.

2. The pressure wire is connected to the system's pressure analyzer and zeroed to atmospheric pressure on the table.
3. The wire is advanced through the guide to the coronary ostium. The pressure wire and guide pressures are matched (i.e., equalized, also called normalized), usually near the tip of the guide.
4. The wire is then advanced across the stenosis about 2 cm distal to the coronary lesion.
5. The NHPR can then be obtained after waiting 45 to 60 seconds for contrast and saline flush hyperemia to abate. The NHPR is measured in duplicate.
6. The contrast FFR or the adenosine FFR are measured at the lowest pressure P_d/P_a , which reflects maximal hyperemia induced by either contrast media or by IV adenosine (140 μg/kg/min) or IC bolus adenosine (50–100 μg for the RCA and 100–200 μg for the left coronary artery). Alternative hyperemic agents are provided in [Table 15.2](#). FFR is the lowest P_d/P_a ratio after the onset of adenosine hyperemia; it usually occurs within 2 minutes for IV adenosine and at 15 to 20 seconds after IC adenosine or 10 cc of contrast media.
7. Based on the FFR/NHPR value, PCI can be performed using the pressure wire as the working angioplasty guidewire.
8. After the stent implantation or diagnostic lesion assessment, FFR/NHPR with pressure pullback can be measured to assess the adequacy of the intervention and impact of any residual disease or hidden lesions in the target or other vessels. At the end of the measurements, the pressure wire should be pulled back into the guide to confirm the absence of pressure drift.

Among the pitfalls and errors of measurement, guide pressure damping, failure to capture the smart minimum P_d/P_a , and signal drift are the most important and most common ([Figure 15.12](#)). [Table 15.3](#) lists several factors that can reduce the accuracy of FFR and NHPR measurements. [Table 15.4](#) provides the approach to common pitfalls and their resolution for coronary physiologic measurements.

FIGURE 15.11 Diagram of hypothetical left main (LM) fractional flow reserve (FFR) and the potential change that might occur when the myocardial bed (yellow overlaid regions) is made smaller (right panels). **A**, Isolated LM narrowing, no left anterior descending coronary artery (LAD), circumflex artery (CFX), right coronary artery (RCA) stenoses. For illustration, the FFR is assigned 0.78. The FFR reflects the physiologic significance of just the LM narrowing. **B**, LM narrowing plus LAD stenosis. LM FFR rises to 0.82 because the LM bed is decreased because of the LAD stenosis. The same scenario would apply when adding LCX narrowing. The LM FFR alone cannot be accurately measured when the myocardial bed flow is compromised. If the LAD and CFX are hemodynamically insignificant, the LM FFR will be accurate. **C**, LM narrowing plus totally occluded RCA with collaterals from LCA, no LAD/LCX disease. The LM FFR is again assigned 0.78. **D**, After RCA opening with resolution of collateral flow, LM FFR increases to 0.84 because the LM myocardial bed size is reduced.

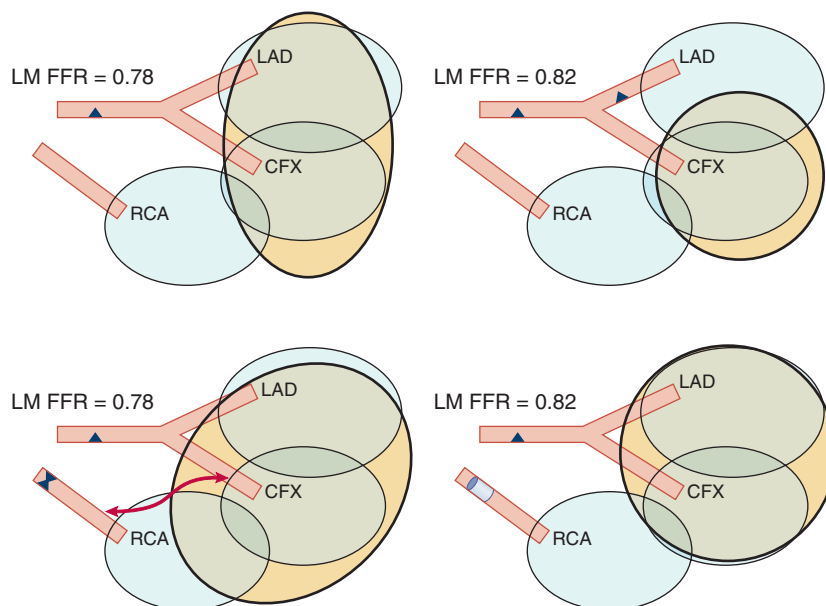


TABLE 15.2 Pharmacologic Characteristics of Agents Used for Induction of Hyperemia

DRUG	DOSE	PLATEAU (s)	HALF-LIFE (min)	SIDE EFFECTS	COMMENTS
Papaverine IC	15 mg LCA 10 mg RCA	30–60	2	Transient Q-T interval prolongation, torsades de pointes	Rarely used
Adenosine IV	140 $\mu\text{g/kg/min}$	60–120	1–2	Decreased blood pressure (10%–15%), chest burning	Avoid in patients with a history of bronchospasm
Adenosine IC	100–200 μg LCA 50–100 μg RCA	5–10	0.5–1	Transient AV block when injected into the dominant artery	Must repeat with escalating doses to ensure that maximal hyperemia is reached
Dobutamine IV	20–40 $\mu\text{g/kg/min}$	60–120	3–5	Tachycardia; increase in blood pressure	May induce ischemia
Nitroprusside IC	0.3–0.9 $\mu\text{g/kg}$	20	1	Decreased blood pressure (20%)	—
Regadenoson IV	0.4 mg	30	2–4 ^a	Tachycardia	Exact length of hyperemia and ability to repeat bolus not studied in the cardiac catheterization lab for FFR

^aHalf-life is triphasic, with second phase lasting about 30 minutes and third phase lasting about 2 hours.

AV, Atrioventricular; FFR, fractional flow reserve; IC, intracoronary; IV, intravenous; LCA, left coronary artery; RCA, right coronary artery.

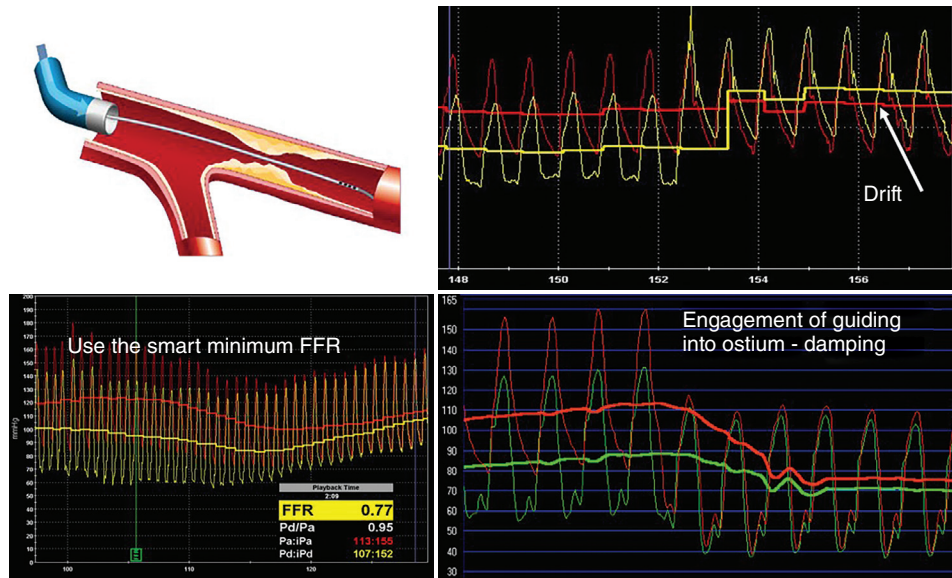


FIGURE 15.12 The three most common errors in the use of fractional flow reserve (FFR)/nonhyperemic pressure ratio (NHPR). *Upper right*, signal drift. The distal pressure wire signal (yellow) has moved above the mean pressure of the guide catheter (red). Often operators accept 0.02 units of drift before resetting the procedures and remeasuring the lesion. *Lower right*, coronary guide catheter pressure damping. On engagement of the guiding catheter into the ostium, the two pressure signals match, resulting in a high or normal distal/aortic mean pressure ratio (P_d/P_a) (right side of the tracing). Before the guide catheter moved (left side of the tracing), the distal pressure can be seen clearly lower than the aortic pressure. Guide catheter damping is recognized on the distorted pressure waveforms during the procedure. *Lower left*, the use of the lowest P_d/P_a ratio during hyperemia is considered the correct and least variable FFR. This point is also called the smart minimum FFR value, which is accurately depicted on most recorder systems as the FFR. Fluctuation of the pressures during intravenous adenosine can be appreciated on this tracing. Using a fixed time point after adenosine infusion may miss the smart minimum FFR.

PHARMACOLOGIC CORONARY HYPEREMIA

The severity of stenosis should always be assessed using measurements obtained during maximal hyperemia. At maximal hyperemia, autoregulation is abolished, and microvascular resistance fixed and minimal. Under these conditions, coronary blood flow is directly related to the driving pressure. Therefore, maximal hyperemic coronary blood flow is closely related to the coronary arterial pressure and is part of the derivation of pressure-derived FFR of the myocardium. The most common hyperemic agent in use today is adenosine.

As a cautionary note, operators should be aware of caffeine use for FFR determinations. Although controversial, caffeine (an adenosine receptor antagonist) may block hyperemia and thereby blunt the true FFR value. A review of the literature suggests that a serum caffeine level of 3 to 4 mg/L

at the time of an adenosine–hyperemia study does not affect the diagnostic ability of myocardial perfusion imaging to detect coronary artery disease (CAD).¹³ Although this likely holds true for patients undergoing IV adenosine-induced hyperemia, if there is any concern, the operator can increase the adenosine dose or use IC adenosine to overcome any receptor inhibition. This issue is not applicable to NHPRs.

VALIDATION OF FRACTIONAL FLOW RESERVE AND NONHYPEREMIC PRESSURE RATIO

Fractional flow reserve values lower than 0.75 are associated with ischemic stress testing with high sensitivity (88%), specificity (100%), positive predicted value (100%), and overall accuracy (93%). FFR values greater than 0.80 are associated with negative ischemic results with a predictive

TABLE 15.3 Technical Factors for Translesional Pressure Measurement Accuracy

1. Equipment factors
 - Erroneous zero
 - Incomplete pressure transmission (tubing or connector leaks)
 - Faulty electric wire connection
 - Pressure signal drift
 - Hemodynamics recorder miscalibration
2. Procedural factors
 - Guide catheter damping
 - Incorrect placement of pressure sensor
 - Inadequate hyperemia (FFR, CFR only)
3. Physiologic factors
 - Serial lesion
 - Reduced myocardial bed
 - Acute MI
4. Theoretical conditions that might influence FFR
 - Severe LVH
 - Exuberant collateral supply
 - Adenosine insensitivity (FFR, CFR only)

CFR, Coronary flow reserve; FFR, fractional flow reserve; LVH, ventricular hypertrophy; MI, myocardial infarction.
Modified from Koolen JJ, Pijls NHJ. Coronary pressure never lies. *Cathet Cardiovasc Intervent*. 2008;72:248-256.

accuracy of 95%. The initial FFR validation study^{3,4} compared FFR with a panel of three different stress tests in the same patients both before and after PCI and remains the most rigorous study of any ischemic diagnostic test. Furthermore, because perfusion scintigraphy compares relative and not absolute myocardial flow in different coronary beds, scintigraphy has difficulty identifying the hemodynamic significance of individual lesions in patients with multivessel CAD. Similarly, on stress echocardiography, severe ischemia in one region may mask the consequences of a less severe albeit hemodynamically significant lesion in another region. Single stress testing comparisons with variations in testing methods and patient cohorts have produced overlapping positive and negative FFR results (0.75–0.80). The interpretation of FFR values in this range requires clinical judgment. In contrast to noninvasive tests, FFR is a vessel- and lesion-specific index of ischemia.

Fractional flow reserve was validated against several ischemic tests in the same individual to establish the threshold for ischemia (Figure 15.13). iFR was initially validated against FFR and subsequently found to have a threshold value of 0.89, which significantly correlated

with FFR (>80%) in large multicenter, multivariate analysis and demonstrated a good diagnostic performance in identifying FFR-positive coronary stenoses. iFR and FFR have similar diagnostic efficiency for detection of ischemia-inducing stenoses when tested against a third comparator¹⁴ (Figure 15.14). Table 15.5 lists ischemic thresholds for IC physiologic measurements.

DISCORDANCE BETWEEN NONHYPEREMIC PRESSURE RATIO AND HYPEREMIC INDICES

Discordance between iFR and FFR occurs in 20% of cases. There are three common situations when one might expect FFR and NHPRs to be discordant: (1) conditions associated high flow (LAD, large myocardial mass, high cardiac output [CO]) favors FFR+/NHPR-, (2) focal lesions favor FFR+/NHPR- because the separation coefficient (sQ^2) is larger in focal than in diffuse lesions, and (3) diffuse lesions favor FFR-/NHPR+ because of lower net CFR. In summary, most of the iFR/FFR+ disparity is due to high translesional flow with high CFR, whereas the converse (iFR+/FFR-) has been seen more in diffuse coronary disease with lower CFR¹⁵ (Figure 15.15). The clinical significance of discordant FFR–NHPR remains under study. In the instantaneous wave-free ratio discordance in intermediate coronary stenoses assessed by FFR (IRIS-FFR) registry, Cook et al.¹⁶ found that adverse clinical event rates are highest when both values are concordantly abnormal (iFR+/FFR+) with lower event rates for discordant iFR+/FFR-, iFR-/FFR+. Concordantly negative iFR-/FFR- are associated with the best outcomes for medical therapy.

To provide more confidence in the decision in this setting, it is recommended to proceed in a step-wise fashion from the NHPR to cFFR and/or to adenosine FFR for a final decision on revascularization.

FRACTIONAL FLOW RESERVE/ NONHYPEREMIC PRESSURE RATIO FOR SPECIFIC ANGIOGRAPHIC SUBSETS

Kogame et al.¹⁷ provide an excellent summary of indices and outcomes related to their use in clinical practice. In patients with stable chronic ischemic heart disease, it is

TABLE 15.4 Common Pitfalls of Coronary Physiology Measurements

ISSUE	IMPACT	RESOLUTION	COMMENT
Preprocedure medications: heparin, nitrates	Omission of heparin: thrombosis Omission of nitrates: vasospasm	Ensure IV heparin 70 u/kg; give IC NTG (100–200 μg) before guidewire insertion	ACT >250 s Vasospasm = ↓ P_d = ↓ FFR, stenosis severity overestimated
Tracing verification missed: correct zero, wire introducer leak, guide damping	Incorrect P_d/P_a	Recheck zero, remove wire introducer, review pressure waveforms	Recheck for drift at end of measurements
Ostial lesion	Damped units pressure; P_d/P_a falsely high	IV hyperemia if FFR used; measurements with guide unseated	Do not use side hole guides; pseudostenosis through side holes
Diffuse disease, serial lesions	Single-point FFR may be erroneous; FFR challenge for serial lesions	Use co-registration pullback with NHPR	iFR >FFR for serial lesions
FFR fluctuates with IV adenosine	Large variability of P_d/P_a during IV adenosine infusion	Use smart minimum FFR	All recorders select the lowest P_d/P_a during hyperemia as correct FFR

ACT, activated clotting time in seconds; Ao, aortic; FFR, fractional flow rate; IC, intracoronary; iFR, instantaneous wave-free ratio; IV, intravenous; NHPR, nonhyperemic pressure ratio; NTG, nitroglycerin; P_d/P_a , distal/aortic mean pressure ratio.

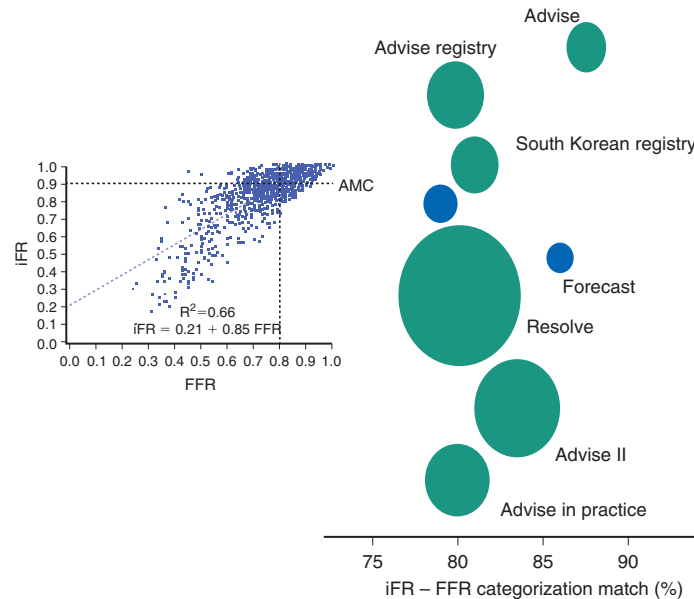


FIGURE 15.13 Validation of fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR). *Left panel*, the plot of the iFR against FFR from the RESOLVE study. *Right panel*, circles represent different studies of instantaneous wave-free ratio (iFR)/FFR with the size of the circle representing the size of the study population. Individual studies demonstrated an 80% to 85% concordance between FFR and iFR. (Right panel from Jeremias A, Maehara A, Génèreux P, et al., Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. *J Am Coll Cardiol*, 2014;63(13):1253-1261.)

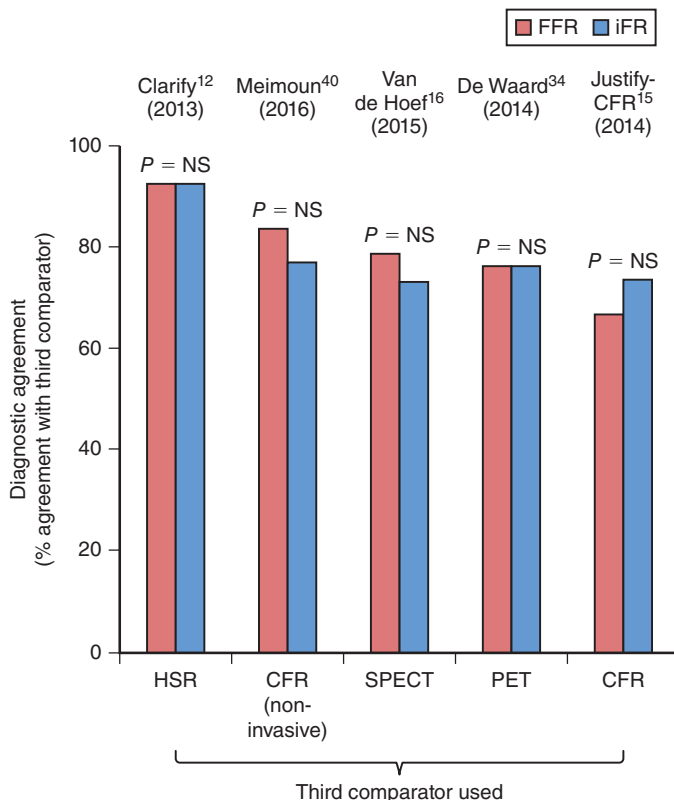


FIGURE 15.14 The bar graph reports the percent agreement of instantaneous wave-free ratio (instantaneous wave-free ratio [iFR]; white boxes) and fractional flow reserve (FFR; black boxes) to the third comparators used in single studies. CFR, Coronary flow reserve; HSR, hyperemic stenosis resistance; PET, positron emission tomography; SPECT, single-photon emission computed tomography. (Adapted from De Rosa S, Polimeni A, Petraco R, Davies JE, Indolfi C. Diagnostic performance of the instantaneous wave-free ratio: comparison with fractional flow reserve. *Circ Cardiovasc Interv*. 2018;11(1):e004613.)

TABLE 15.5 Ischemic Thresholds for Intracoronary Physiologic Measurements

HYPEREMIC PRESSURE RATIOS	THRESHOLD
Adenosine FFR	≤ 0.80
Contrast FFR	~0.83
Nonhyperemic Pressure Ratios	
Distal coronary pressure/proximal coronary pressure (P_d/P_a)	≤ 0.91
Resting full-cycle ratio (RFR)	≤ 0.89
Diastolic hyperemia-free ratio (DHR)	≤ 0.89
Instantaneous wave-free ratio (iFR)	≤ 0.89
Diastolic pressure ratio (dPR)	≤ 0.89
Diastolic pressure ratio (DPR):	≤ 0.89
Coronary Doppler	
Coronary flow reserve (CFR)	<2.0
Proximal to distal flow velocity ratio (P/D)	<1.7
Diastolic to systolic velocity ratio (DSVR)	<1.8
Indices of Coronary Microvascular Disease	
Coronary flow reserve (CFR; Doppler or thermodilution)	<2.0-2.5
Index of microvascular resistance (IMR; distal pressure/(1/mean transit time) at maximal hyperemia)	≥25 U

safe to defer stenting of an angiographically intermediately narrowed stenosis (30%–70% visual diameter), which is hemodynamically insignificant (FFR >0.75). The 15-year outcome of the Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis (DEFER) study found that patients having an intermediate lesion (>50% narrowing) and FFR greater than 0.75 could be safely treated medically. Their event rate over 15-year follow-up was no greater than any patient with stable ischemic heart disease treated medically (~4%/year event rate) compared with the patients with intermediate lesions who were stented despite an FFR

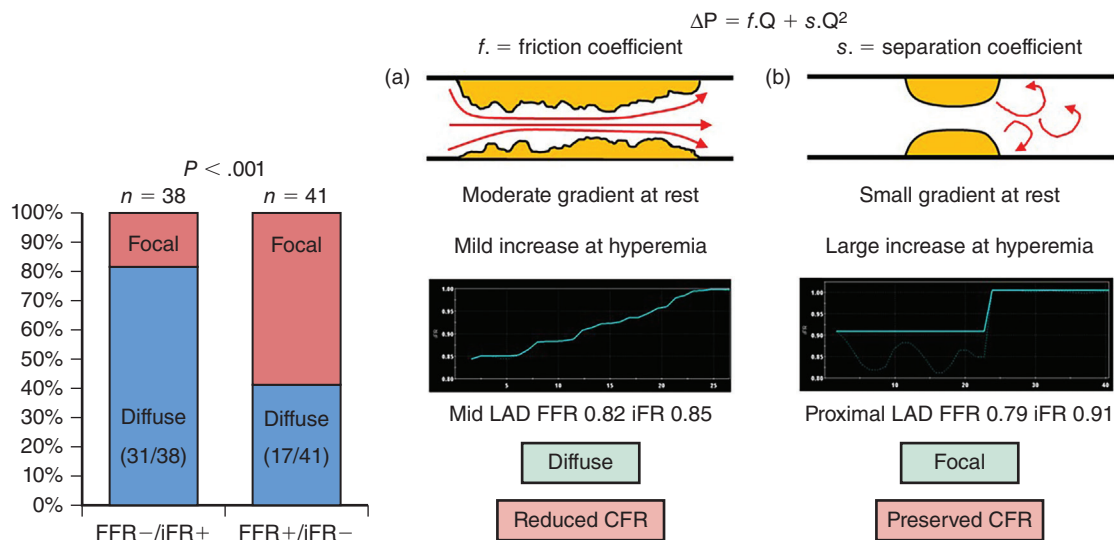


FIGURE 15.15 Disease patterns of instantaneous wave-free ratio (iFR)-fractional flow reserve (FFR) discordance. The coefficient of friction for diffuse disease contributes to discordance between FFR- and iFR+; however, in focal lesions, the separation coefficient plays a larger role, and thus FFR+/iFR- is more common. FFR will be likely positive when iFR may be negative. There is also an association of reduced coronary flow reserve (CFR) with the FFR-/iFR+, and with preserved CFR, FFR+/iFR- is more common. LAD, Left anterior descending coronary artery. (From Warisawa T, Cook CM, Howard JP, et al. Physiological pattern of disease assessed by pressure-wire pullback has an influence on fractional flow reserve/instantaneous wave-free ratio discordance. *Circ Cardiovasc Interv.* 2019;12(5):e007494.)

greater than 0.75 and patients with an FFR less than 0.75, each group having incrementally higher events over time. Stenting lesions that are not hemodynamically significant has the potential to produce new problems related to the stent procedure or late stent adverse events (subacute thrombosis, bleeding risk from dual antiplatelet medications). For the deferred and performed groups, the event-free survival rate was the same (80% and 73%, respectively; $P = .52$), and both were significantly better than in the reference (abnormal FFR, stented) group (63%; $P = .03$). The composite rates of cardiac death and acute MI in the deferred, performed, and reference groups were 3%, 8%, and 16%, respectively ($P = .21$ for deferred versus performed and $P = .003$ for reference versus both the deferred and performed groups) (Figure 15.16). The percentage of patients free from chest pain on follow-up was not different between the deferred and performed groups. FFR-guided treatment of patients with intermediate lesions is associated with a low event rate, comparable to event rates in patients with normal noninvasive testing results.

MULTIVESSEL DISEASE PERCUTANEOUS CORONARY INTERVENTION

Fractional flow reserve-guided multivessel PCI demonstrated lower major adverse cardiovascular events (MACEs) than the conventional angiographically guided approach in the FAME (FFR Versus Angiography for Multivessel Evaluation) trial by¹⁸ FAME compared a physiologically guided PCI approach (FFR-PCI) with a conventional angiographic-guided PCI (angio-PCI) in patients with multivessel CAD. A total of 1005 patients with multivessel CAD undergoing PCI with drug-eluting stents (DESs) were enrolled. Operators identified all lesions by visual angiographic appearance (>50% diameter stenosis) to be treated in advance of randomization to a stenting strategy. For the FFR-PCI group

($n = 496$), all lesions had FFR measurements, and only those with an FFR less than 0.80 were stented. For the angio-PCI group ($n = 509$), all lesions identified were stented. Clinical characteristics and angiographic findings were similar in both groups, with average SYNTAX scores of 14.5 (indicating low- to intermediate-risk patients).

Compared with the angio-PCI group, the FFR-PCI group used fewer stents per patient (1.9 ± 1.3 vs 2.7 ± 1.2 ; $P < .001$) and less contrast (272 mL vs 302 mL; $P < .001$) and had a lower procedure cost (\$5332 vs \$6007; $P < .001$) and shorter hospital stay (3.4 vs 3.7 days; $P = .05$). More important, the 2-year rates of mortality or MI were 13% in the angio-PCI group compared with 8% in the FFR-PCI group ($P = .02$). Composite rates of death or nonfatal MI or revascularization were 22% and 18%, respectively ($P = .08$). For lesions deferred based on an FFR of greater than 0.80, the rate of MI was only 0.2%, and the rate of revascularization was 3.2% after 2 years (Figure 15.17).

The FAME trial demonstrated that PCI guided by FFR in patients with multivessel CAD significantly reduces mortality rates and MI at 2 years compared with standard angiography-guided PCI. A related cost-effectiveness evaluation showed that FFR-guided PCI not only improved outcomes but also did so at a significantly lower cost.

Like the Ischemia trial, patients with positive ischemic FFR values (<0.80) have fewer events after revascularization than those remaining on optimal medical therapy (OMT) alone for patients with multivessel CAD. The FAME 2 (Fractional Flow Reserve-Guided PCI Versus Medical Therapy in Stable Coronary Disease) trial compared OMT with PCI in patients with proven ischemia by FFR. A total of 1220 patients with angiographic disease in one, two, or three vessels that was suitable for PCI underwent FFR. All patients with lesions having an FFR of 0.80 or less were randomized to either PCI or medical therapy alone. A composite of all-cause mortality, nonfatal MI, or unplanned hospitalization leading to urgent revascularization during a

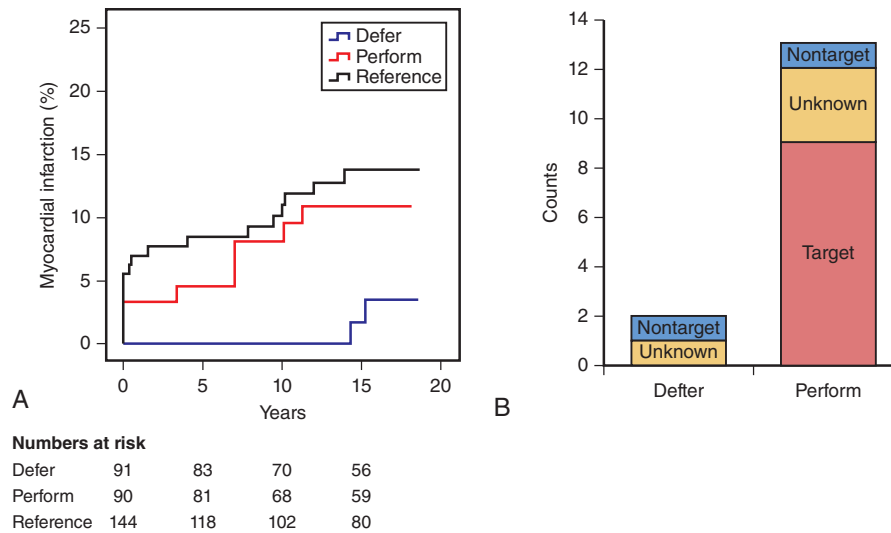


FIGURE 15.16 Fifteen-year follow-up of patients in the DEFER trial. **A**, Event rates of myocardial infarction (MI) and death for patients in the normal fractional flow reserve (FFR) in the defer group treated medically (blue), patients with normal FFR but who were stented (red), and patients with abnormal FFR who were stented (black). **B**, Number of patients in the defer and perform groups having events in the target vessel, another vessel, or an unknown site. Right panel, comparison of the vessel relationship with MI with vessel territory. (From Zimmermann FM, Ferrara A, Johnson NP, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J*. 2015;36(45):3182-3188.)

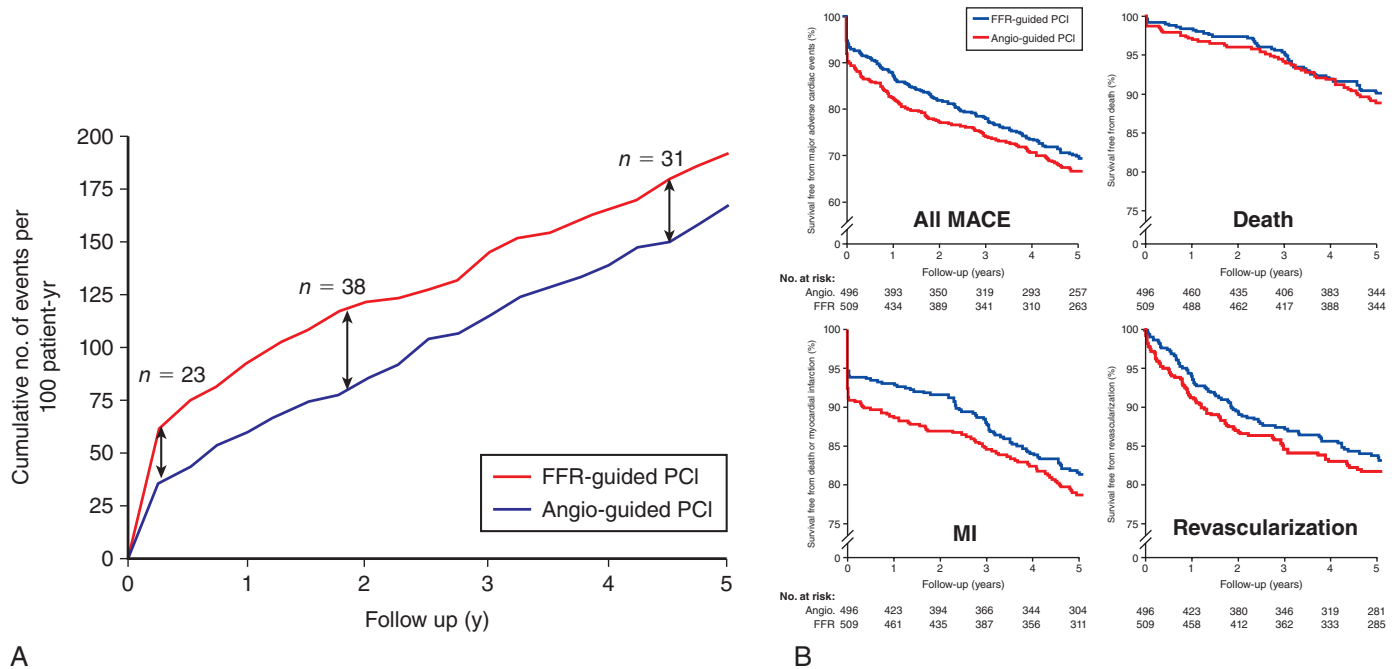


FIGURE 15.17 FAME (FFR Versus Angiography for Multivessel Evaluation) 5-year follow-up event rates. **A**, Cumulative event rates over 5 years comparing fractional flow reserve (FFR)-guided compared with angiographically guided percutaneous coronary intervention (PCI). **B**, Kaplan-Meier event curves over 5 years for major adverse cardiovascular events (MACEs), death, myocardial infarction (MI), and revascularization. (Data from Presented at European Society of Cardiology, August 2015 by Dr. Nico Pijls.)

2-year follow-up was the primary endpoint. As in prior studies following those lesions that did not undergo PCI for an FFR greater than 0.80, in the FAME 2 trial, lesions that had FFR values greater than 0.80 were entered into a registry and followed. These patients had a low rate of the primary endpoint of death (0%), MI (1.8%), or urgent revascularization (2.4%) over the follow-up 12 months, thus reproducing the findings of the pre-DES era DEFER trial.

These foundational FFR trials reinforce the concept that for coronary stenoses whose FFR is not physiologically significant (i.e., >0.80), revascularization will not improve their good prognosis with OMT.

NONHYPEREMIC PRESSURE RATIO AND INTERMEDIATE LESION ASSESSMENT

Comparative studies showed that iFR has an 80% correspondence with FFR (see Figure 15.13). The two largest randomized noninferiority trials of iFR and FFR are the functional lesion assessment of intermediate stenosis to guide revascularisation (DEFINE-FLAIR)¹⁹ and the instantaneous wave-free ratio versus fractional flow reserve to guide PCI-swedeheart registry (iFR-SWEDEHEART)²⁰ trials in which participants were randomized to iFR or FFR-guided PCI or medical therapy. The DEFINE-FLAIR

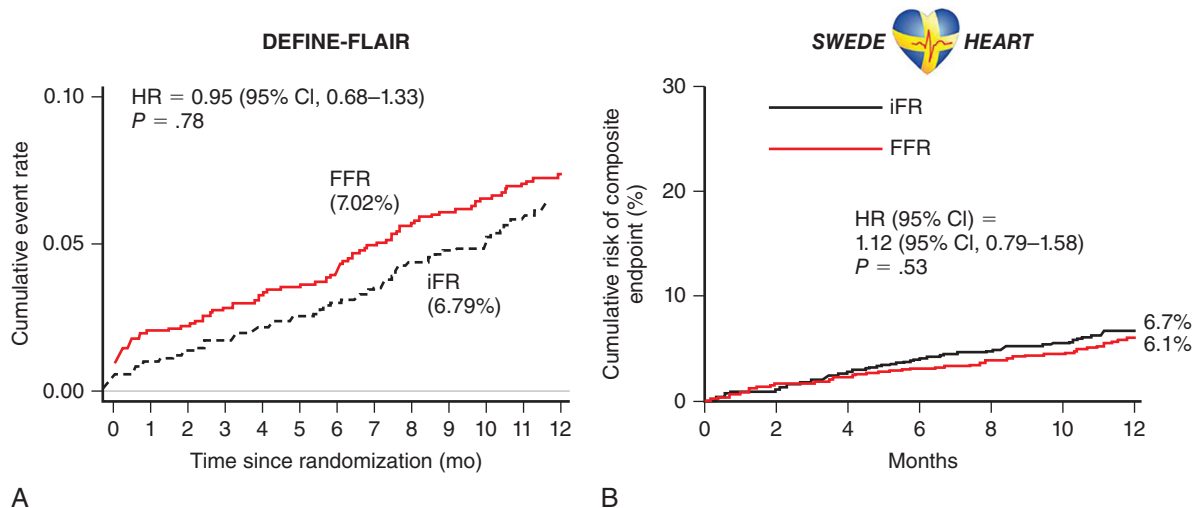


FIGURE 15.18 The DEFINE-FLAIR (A) and SwedeHeart (B) trials demonstrated noninferiority for instantaneous wave-free ratio (iFR) against fractional flow reserve (FFR)-guided percutaneous coronary intervention. HR, Hazard ratio; DEFINE-FLAIR, functional lesion assessment of intermediate stenosis to guide revascularisation. (From Davies JE, Sen S, Dehbi HM, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med*. 2017;376(19):1824-1834; Göteborg M, Christiansen EH, Gudmundsdottir IJ, et al; iFR-SWEDEHEART Investigators. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med*. 2017;376(19):1813-1823. doi:10.1056/NEJMoa1616540.)

investigators enrolled 2492 patients at 49 centers in 17 countries. The iFR-SWEDEHEART researchers enrolled 2037 patients at 15 centers in Sweden, Denmark, and Iceland. A total of 2019 patients in this study were treated according to protocol. At 1 year, there were no significant differences between iFR and FFR for the composite primary endpoint of all-cause mortality, MI, or revascularization. Both studies showed reduced chest discomfort and procedure times as would be expected by the administration of IV adenosine as the major methodologic difference between iFR and FFR.

In the iFR-SWEDEHEART trial, significant lesions were found in 29% of patients undergoing iFR and 37% undergoing FFR. A similar pattern was present in DEFINE-FLAIR. From multicenter randomized trials, the dichotomous threshold of iFR below 0.89 produces noninferior clinical outcomes when compared with FFR below 0.80 (Figure 15.18). NHPR is now in common use because it streamlines the workflow for coronary lesion assessment principally because it obviates need for hyperemia.

LEFT MAIN STENOSIS

Because of the inherent limitations of angiography, visual assessment alone is often not reliable to characterize the clinical significance of a left main (LM) artery narrowing, and thus translesional physiology becomes particularly valuable for accurate decision making before CABG. The largest study with a 5-year outcome was reported by Hamilos et al.²¹ in which 213 patients with an angiographically equivocal LM coronary artery stenosis were treated medically if the FFR was above 0.80 (nonsurgical group; $n = 138$) and underwent revascularization (surgical group; $n = 75$) if the FFR was below 0.80. The 5-year survival estimates were 90% in the nonsurgical (FFR >0.80) group and 85% in the surgical (FFR <0.80) group ($P = .48$). The 5-year event-free survival estimates were 74% and 82% in the two groups,

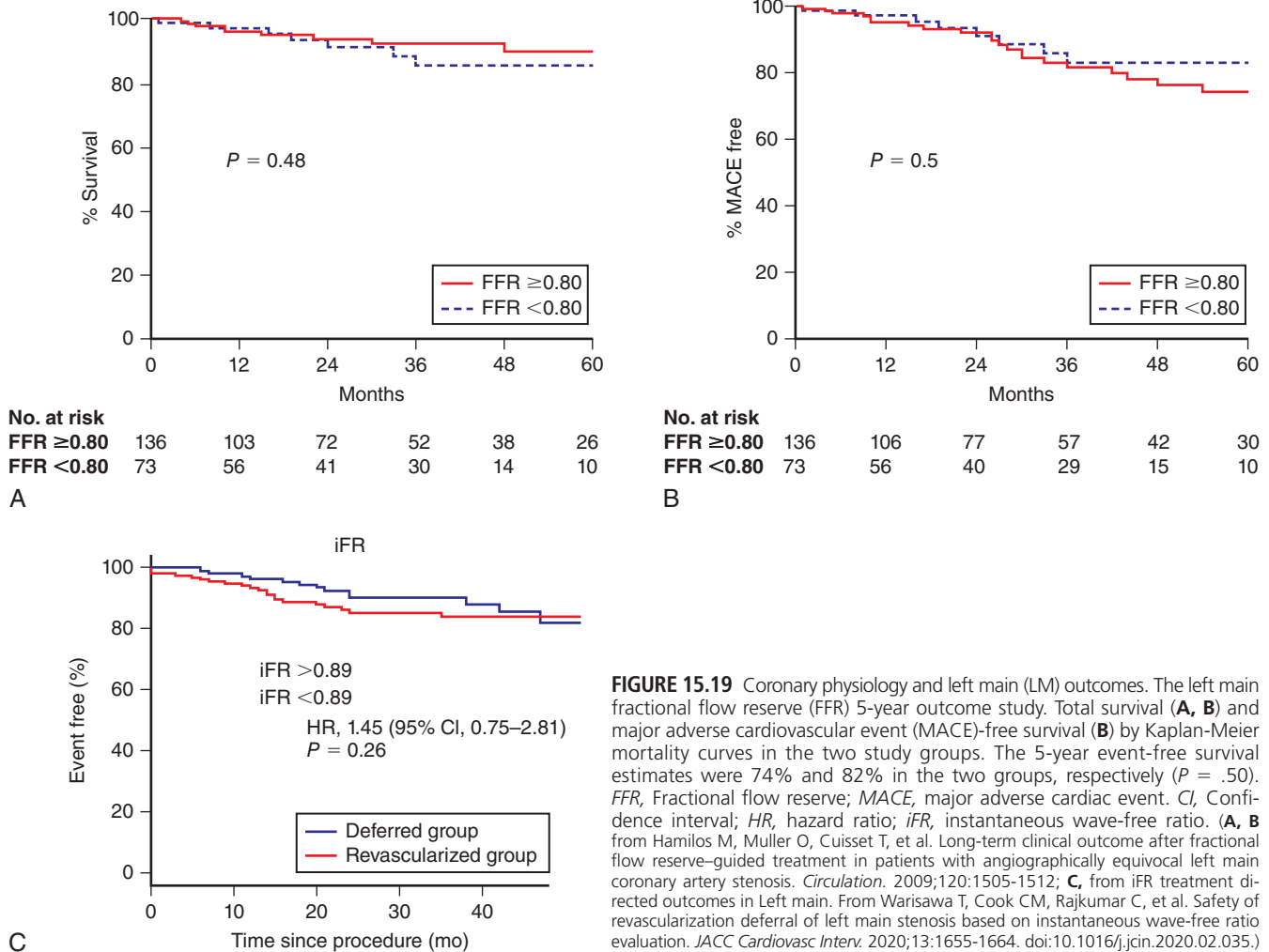
respectively ($P = .50$) (Figure 15.19). Of note, only 23% of patients with a diameter stenosis greater than 50% had a hemodynamically significant LM by FFR.

Warisara et al.²² examined iFR and LM stenosis in a multicenter observational study of 314 patients. Based on an iFR threshold of 0.89, LM stenosis was deferred ($n = 163$) or revascularized ($n = 151$). At a median follow-up period of 30 months, MACE occurred in 15 patients (9.2%) in the deferred group and 22 patients (14.6%) in the revascularized group ($P = .26$). There was no difference between the medical or revascularized groups. In the iFR-based deferral and revascularization groups, results were as follows: all-cause death, 3.7% versus 4.6%; cardiac death, 1.2% versus 2.0%; nonfatal MI, 2.5% versus 5.3%; and target lesion revascularization, 4.3% versus 5.3% ($P > .05$ for all). Although the number of iFR-LM studies is limited, the deferral of revascularization of LM stenosis based on iFR appears to be safe, with similar long-term outcomes to those who were revascularized. Figure 15.19 shows FFR and iFR LM outcomes.

See Video 15.1 for case example of a patient with LM stenosis assessed with FFR.

A simple, isolated LM stenosis is easily assessed by FFR in the routine fashion. A distal LM bifurcation stenosis can be assessed with two FFR/NHPR measurements, one in the LAD and another with the pressure wire in the circumflex artery (CFX). For FFR, however, interpreting the LM FFR in the presence of significant downstream branch lesions is more complicated because the LM and LAD and CFX lesions act like serial lesions. The true flow across the LM is potentially reduced by a severe downstream stenosis, artifactually elevating the LM FFR when measured in the unobstructed vessel.

For an accurate FFR, maximal hyperemia must be achieved across the LM stenosis. Flow through the LM artery is the sum of the LAD CFX branch flow, the magnitude of flow being proportional to the size of each artery's viable myocardial bed. When LM FFR is measured in the unobstructed CFX artery, the reliability of this measurement



will depend on whether the LAD stenosis is severe enough to impair flow. The lower LM flow would produce an erroneously elevated FFR because true maximal hyperemia would not be achieved (see Figure 15.11).

In practice, the LM FFR in the setting of LM and LAD disease is assessed by placing the pressure wire sensor distal to the LAD lesion, administering adenosine hyperemia (either IV or IC), and calculating the FFR across both lesions, which is called the $FFR_{epicardial}$. If $FFR_{epicardial}$ is greater than 0.80, neither lesion is physiologically significant, and no further intervention is needed. However, if the $FFR_{epicardial}$ is 0.80 or less, the operator can measure FFR in the CFX. An apparent LM FFR (FFR_{app}) in the CFX of greater than 0.80 would seem to indicate that the LAD but not the LM is hemodynamically significant. However, this is not always correct. A disadvantage of this assumption is that after the LAD lesion is stented, LM flow increases and the FFR_{app} may now become significant, mandating further revascularization. If unprotected LM stenting is not planned, performing PCI of a downstream LAD lesion, which would lead to a significantly abnormal LM FFR, may not be the best option.

Fearon et al.²³ identified that the location and severity of downstream lesion determines whether FFR_{app} is accurate.

To validate this concept, a model of a complex LM and LAD stenosis was created in patients in the catheterization laboratory after LAD stenting. An intermediate LM stenosis was created by positioning a partially deflated balloon catheter in the normal LM and another balloon catheter in the newly stented LAD, each over a pressure wire. Increasing the severity of the LAD lesion showed that the true LM FFR (FFR_{true}), measured in the nondiseased (i.e., CFX) vessel, increased (i.e., higher FFR) during LAD balloon inflation. The FFR_{true} was statistically but clinically insignificantly lower than FFR_{app} (0.81 ± 0.08 vs 0.83 ± 0.08 ; $P < .001$), a difference that correlated with the severity of the downstream disease ($r = 0.35$; $P < .001$). In all cases in which FFR_{app} was greater than 0.85, the FFR_{true} was greater than 0.80. The important observation of this study was that the FFR_{true} was significantly lower than FFR_{app} only when downstream stenoses in the LAD (or LCF) were very severe with $FFR_{epicardial}$ less than 0.60. In these situations, an intravascular ultrasound assessment of the LM with a threshold minimal luminal area of less than 6.0 mm^2 is recommended. The reliability of the LM FFR depends on operator technique, accurate hemodynamic signal acquisition, and adequate maximal hyperemia (Figure 15.20).

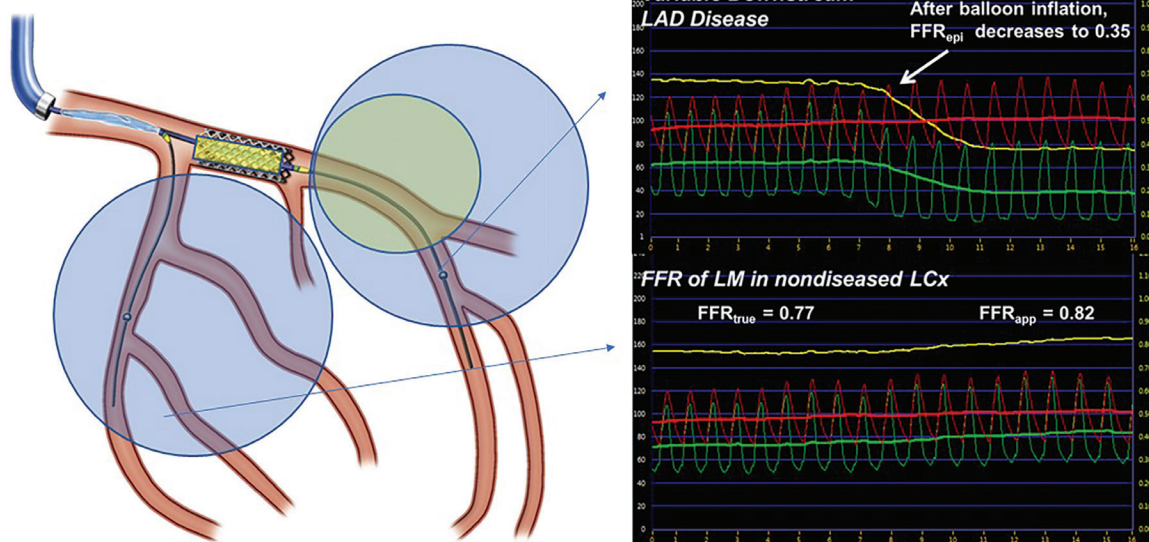


FIGURE 15.20 Impact of distal left anterior descending coronary artery (LAD) stenosis on apparent fractional flow reserve (FFR) in the left main (LM) artery. The model used in patients who had LAD stent placement used a second partially inflated balloon in the LM to simulate an intermediate LM lesion. Two pressure wires were used and measured FFR in the LAD and circumflex (LCx) zones (large blue circles); the arrows connect the bed (blue circle) to their respective FFR tracings; yellow line in the right panel). As the LAD balloon is inflated, the LAD territory diminishes (yellow circle), and the FFR in the circumflex as the apparent FFR of the LM rises indicating depending on myocardial bed size to produce an accurate FFR of the LM. Only a very severe lesion ($\text{FFR} < 0.60$) will increase the LM $\text{FFR}_{\text{apparent}}$. (From Fearon WF, Yong AS, Lenders G, et al. The impact of downstream coronary stenosis on fractional flow reserve assessment of intermediate left main coronary artery disease: human validation. *J Am Coll Cardiol Interv.* 2015; 8(3):398-403.)

SERIAL (MULTIPLE) LESIONS AND DIFFUSE CORONARY ARTERY DISEASE

The interaction between the stenoses prevents the use of the FFR ratio (P_d/P_a) for each stenosis individually. The first lesion blunts the hyperemia of the second and vice versa. Moreover, the extent of this interaction is unpredictable. The individual FFR of each stenosis separately can be predicted by a different FFR equation from Pijls et al.²⁴ using P_a , pressure between the two stenoses (P_m), P_d , and coronary occlusion wedge pressure (P_w) during maximum hyperemia:

$$\text{FFR}_{\text{predicted}} = (P_d - [(P_m / P_a) * P_w]) / ((P_a - P_m) + (P_d - P_w))$$

This calculation requires the use of the P_w during balloon inflation, an impractical method for routine diagnostic measurements.

The use of pullback pressure tracings from distal to proximal at rest or during hyperemia provides more information and a more accurate method to determine the hemodynamic significance of multiple lesions in series or in the setting of diffuse disease. Using iFR to assess serial lesions is easier than FFR and may prove to be the preferred clinical approach. Kikuta et al.²⁵ presented the value of iFR pullback measurements before angioplasty, assessing how often the treatment strategy based on angiography alone was changed and predicting the post-PCI hemodynamic result. In 168 lesions, the iFR pullback procedure identified the relative ischemic contribution of each stenosed segment to the iFR value of the entire vessel. This information changed the revascularization plan 31% of the time with a reduction in the average number and length of stents implanted. At the same time, the pre-PCI iFR

pullback method was used to predict the post-PCI iFR measurement in 134 vessels (128 patients). After PCI, the mean difference between predicted and actual post-PCI iFR was small at 0.011 ± 0.004 with a strong correlation ($r = 0.73$; $P < .001$). iFR pullback may help in determining the adequacy of stent placement. By assuming constant resting flow, the ratio of pressures over the whole vessel (total iFR) should be the sum of the pressure losses across each stenosis (ΔiFR). Thus, removing one or more stenoses by PCI increases the total iFR by the ΔiFR generated by the treated stenosis. The angiographic co-registration of NHPR (e.g., iFR) will improve the way PCI is performed and improve outcomes by reducing the residual and unsuspected ischemia. Figure 15.21 is an example of iFR co-registration identifying lesions appropriate for revascularization.

DIFFUSE CORONARY DISEASE

The pressure pullback recording at maximum hyperemia will provide the necessary information to decide if and where stent implantation may be useful. The location of a focal pressure drop superimposed on the diffuse disease can be identified as an appropriate location for treatment. Diffuse CAD can produce an abnormal FFR in the absence of focal epicardial stenoses and might be best treated medically or with surgical revascularization. Using FFR during continuous pressure wire pullback from a distal to proximal location, the impact of diffuse atherosclerosis can be documented. Diffuse atherosclerosis, rather than a focal narrowing, is characterized by a continuous and gradual pressure recovery during pullback, without any abrupt increase in pressure related to a focal region²⁶ Figure 15.22 shows the use of a pullback pressure gradient index.

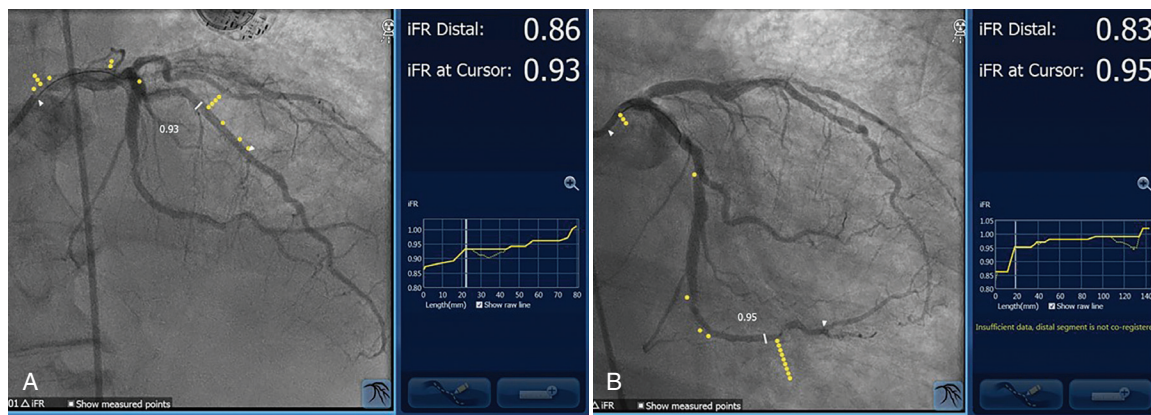


FIGURE 15.21 Simultaneous angiographic co-registration of instantaneous wave-free ratio (iFR). localizes and differentiates diffuse from focal disease in an 81-year-old man with angina and dyspnea. The patient had a stent placed in the circumflex (CFX) artery 4 years ago. The result from an exercise stress test 1 year ago was negative. The *yellow dots* overlying each angiogram correspond to the location of a 0.01 iFR pressure drop. **A**, A diffusely diseased left anterior descending artery. The cursor may be moved to any given location in the vessel to determine the estimated iFR at that position. **B**, A focal stenosis in the CFX coronary artery. On pressure pullback, there is a severe focal lesion in the distal circumflex that can easily be seen to differentiate focal from diffuse disease.

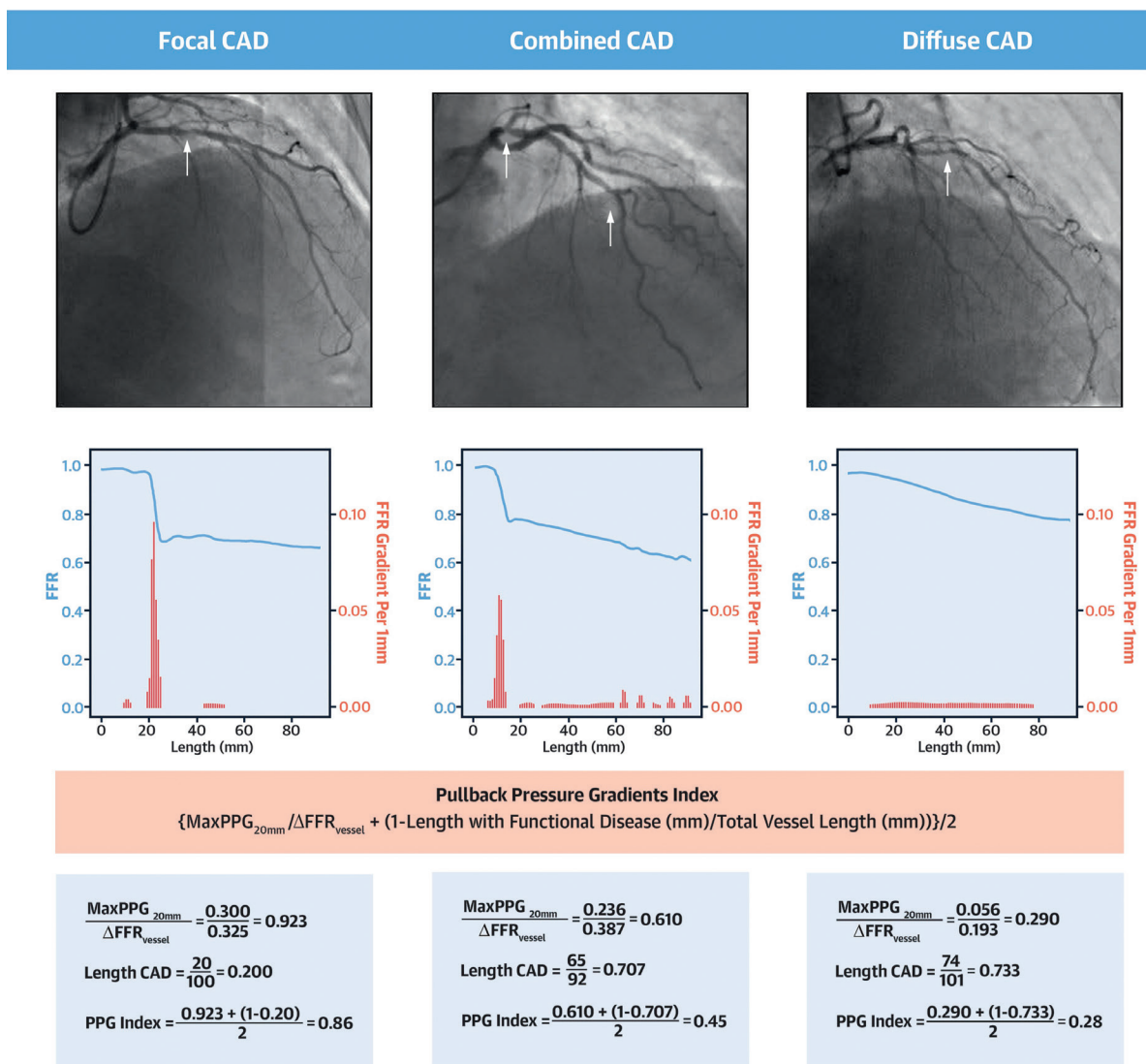


FIGURE 15.22 Pathophysiological coronary artery disease patterns and pressure pullback gradient (PPG) index. Three case examples depicting the pathophysiological patterns of coronary artery disease (CAD). *Top*, Conventional coronary angiography. *Middle*, The fractional flow reserve (FFR) pullback curves and histograms depicting the magnitude and extension of FFR drop. *Bottom*, Details of the PPG calculation. The *red bars* indicate FFR drops of 0.0015 or more. In the *top left panel*, the angiogram shows a severe lesion in the mid left anterior descending coronary artery (LAD) (*white arrow*) with a distal FFR of 0.68. This lesion produced an FFR drop responsible for 86% of the distal FFR with a maximum pullback pressure gradient over 20 mm of 0.30 FFR units. Only 20% of the vessel showed functional disease. The PPG index was 0.86, indicating physiological focal CAD. The top middle panel shows a severe lesion at the proximal LAD and a moderate lesion at the mid LAD (*white arrows*). The maximum pullback pressure gradient over 20 mm was 0.236 FFR units, with 70.7% of the vessel length showing FFR deterioration, and the PPG index was 0.45. In the *top right panel*, an anatomic lesion at the mid LAD (*white arrow*) was observed with distal FFR of 0.78. The maximum pullback pressure gradient over 20 mm was 0.056, but 73.3% of the vessel length showed physiological disease. The PPG index was 0.28, indicating physiological diffuse. (From Collet C, Sonck J, Vandeloo B, et al. Measurement of hyperemic pullback pressure gradients to characterize patterns of coronary atherosclerosis. *J Am Coll Cardiol*. 2019;74:1771-1784.)

Shin et al.²⁷ mapped the pullback pressure along the vessel using an angiographically derived FFR, called quantitative flow ratio (QFR). The physiologic distribution of diffuse disease even without a significant ischemic gradient significantly contributes to worse post-PCI outcomes. Using the pullback pressure gradient index²⁸ and the change in QFR over the length of the lesion to determine whether the lesions were predominantly focal or diffuse, patients were grouped into four distinct disease patterns: two with predominantly focal disease with and without a major gradient (G1 [*n* = 150] and G2 [*n* = 21], respectively) and two with predominantly diffuse disease with and without major gradient (G3 [*n* = 115] and G4 [*n* = 55], respectively). Proportions of suboptimal post-PCI physiologic results were highest in group 4 (56% compared with 19%, 24%, 23% in groups 1, 2, and 3, respectively). Most important, target vessel failure (TVF) was significantly higher in

groups 3 and 4 (diffuse disease with and without major gradients; G3, 8% and G4, 10% vs G1, 1.4% and G2, 0.0%; *P* = .024), meaning that after successful PCI, TVF risk was mainly determined by the distribution (i.e., burden of diffuse disease) rather than focal lesion severity (i.e., the initial gradient). Paradoxically, the highest TVF belonged to those with diffuse disease without a major gradient (group 4) (Figures 15.23 and 15.24).

FRACTIONAL FLOW RESERVE IN ACUTE CORONARY SYNDROME

In acute coronary syndrome (ACS), especially in the acute MI (AMI), the pathophysiology of the infarcted artery and its subtended microvascular bed is complex. The predictive ability of FFR in ACS is limited because

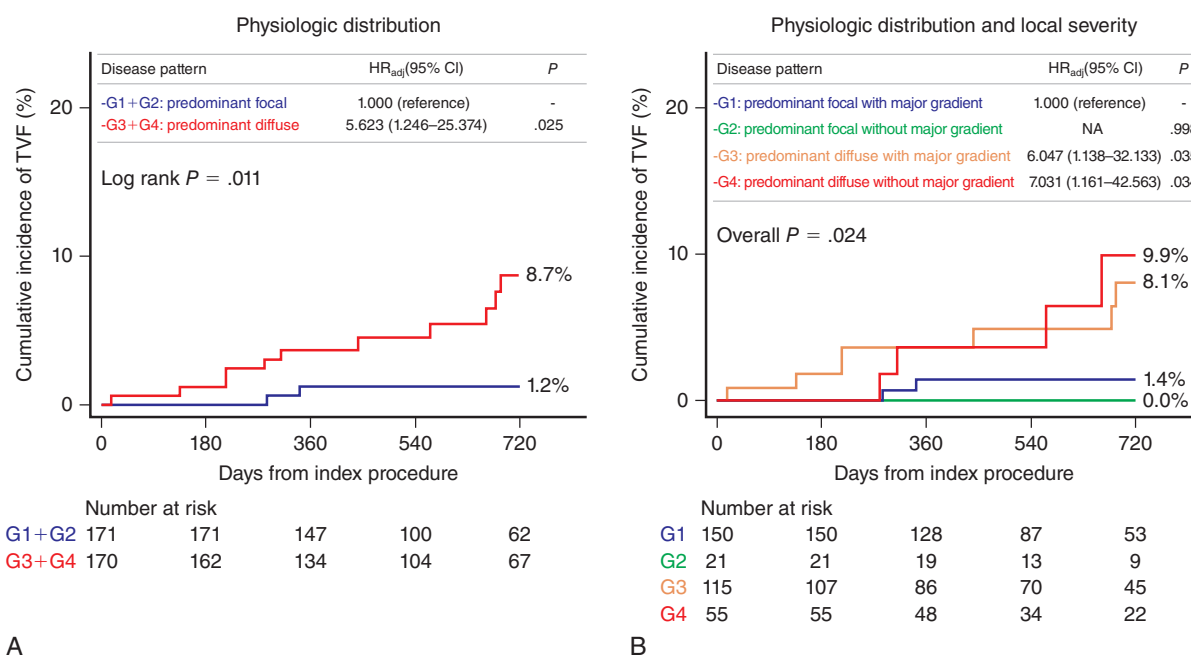


FIGURE 15.23 Comparison of target vessel failure (TVF) at 2 years after successful percutaneous coronary intervention (PCI). According to pre-PCI disease patterns determined by quantitative flow ratio (QFR) pressure pullback gradient (PPG) index and change in quantitative flow ratio per change in time (dQFR/ds). The cumulative incidence of TVF at 2 years after successful PCI according to predominant focal or diffuse disease (**A**) and according to the four pre-PCI disease patterns (**B**). Groups 3 and 4 with diffuse disease did worse despite only a small gradient in group 3. CI, Confidence interval; HR_{adj}, adjusted hazard ratio; NA, not available. (From Shin D, Dai N, Lee JM, et al. Physiologic distribution and local severity of coronary artery disease and outcomes after percutaneous coronary interventions. *JACC Interv*. 2021;14(16):1771-1785.)

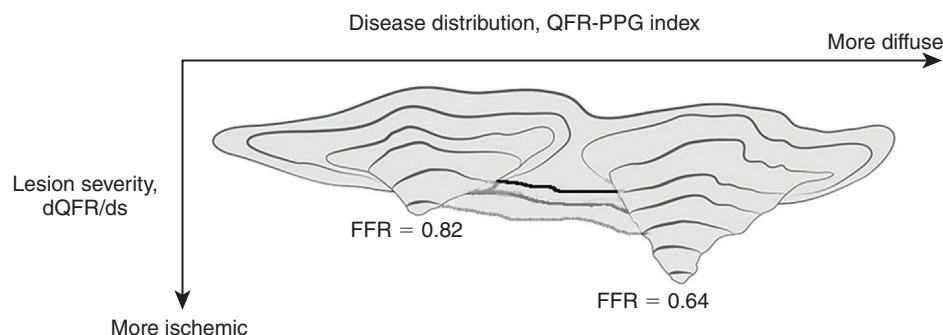


FIGURE 15.24 A topographic map of two-dimensional (2D) physiology with lesion severity on the y-axis and disease distribution along the x-axis. Single-point fractional flow reserve (FFR) values do not provide the complete picture of the patient's risk profile and prognosis. dQFR/ds, change in quantitative flow ratio over change in time. (Modified from Kern MJ. Quantitative flow ratio (QFR), 2D physiologic mapping, and the negative impact of diffuse disease on PCI outcomes. *JACC Cardiovasc Interv*. 2021;14:1786-1788.)

(1) the microvascular bed in the infarct zone may not have uniform, constant, or minimal resistance; (2) the severity of stenosis may evolve as thrombus and vasoconstriction abate; and (3) FFR measurements are not meaningful when normal perfusion (i.e., maximal hyperemia) cannot be achieved. Nonetheless, FFR has demonstrated value in remote lesion assessment and in target lesion assessment during the recovery phase of MI, usually after 48 hours.

In patients with STEMI, complete revascularization remains a principal goal. In the Primulti Study²⁹ comparing culprit-only PCI with complete revascularization with FFR of the non-infarct-related artery, any non-IRA (infarct related artery) considered angiographically significant was treated if the FFR was less than 0.80. There were 313 patients in the culprit-only group and 314 patients with complete revascularization with non-IRA stenting guided by FFR. At a 2-year follow-up MACEs occurred in 68 (22%) patients of the culprit-only group compared with 40 (13%) in the FFR-guided STEMI revascularization group (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.38–0.83; $P = .004$).

Whether FFR is reliable in the ACS setting depends on the extent of impaired myocardium and its potential for recovery. FFR is directly related to flow; flow is directly related to the myocardial territory or mass supplied by the culprit vessel. Thus, for the same stenosis at two points in time, the FFR could decrease if the flow measured later increased because of myocardial bed recovery as might be expected with infarct healing (Figure 15.25).

Because of a changing myocardial bed during recuperation after an acute infarction, FFR is not used in the STEMI culprit artery until 4 to 6 days after the event, when myocardial function is believed to stabilize. For non-IRA in patients with STEMI or non-ST-elevation myocardial infarction (STEMI), the zone of myocardial injury of the culprit vessel is unknown but may extend close to the region supplied by the non-IRA. Theoretically, a normal FFR at the time of STEMI might be lower several days later if the myocardial flow improves to the remote non-IRA zone,

changing the initial treatment decision based on a high FFR. However, FFR appears to be stable over time in non-IRA in patients with STEMI or NSTEMI.²⁶ In a subset of the FAME study, 101 patients undergoing PCI for both STEMI and NSTEMI had 112 non-IRA lesions assessed by FFR at the index procedure and again 35 ± 4 days later. The non-IRA FFR was 0.77 ± 0.13 at baseline and identical at follow-up remeasurement, concluding that in ACS, FFR was unchanged over 3 months after presentation.

Similarly, from the complete revascularization in acute myocardial infarction (COMPARE-ACUTE) multicenter trial³⁰ of multivessel disease and STEMI undergoing primary PCI, 613 FFR measurements were made in non-IRA lesions. FFR results were negative in 57% (>0.80) and positive in 43%, highlighting the fact that non-IRA lesions identified during STEMI may be innocent bystanders and may not need to be treated.

Given the results of the FFR for non-IRA in patients with ACS including STEMI, clinical decisions based on FFR produce durable outcomes and is a viable strategy for revascularization of non-IRA.

POST-PERCUTANEOUS CORONARY INTERVENTION PHYSIOLOGY

Post-PCI functional assessment predicts long-term patient outcomes and provides insights into the residual ischemic potential of the treated vessel. Suboptimal functional results should be examined and treated if possible. Post-PCI physiological patient outcomes are summarized in Figure 15.26A.

The conclusion of a large meta-analysis of 970 lesions from 10 studies found that there was an independent and continuous relationship between post-PCI FFR and MACEs. Hakeem and Uretsky³¹ demonstrated that the higher the final FFR/NHPR, the fewer the adverse events (Figures 15.26 and 15.27). A key concern for interpretation of post-PCI studies is that mechanisms for suboptimal post-PCI physiology are not always evident. As shown in the physiologic assessment of coronary stenosis following PCI (DEFINE-PCI) study,³² 25% of angiographically adequate interventions have residual hemodynamic impairment caused by diffuse CAD, unsuspected new narrowing, edge stent dissection, proximal vessel narrowing, or vasospasm (Figure 15.28). Fournier et al.³³ investigated the prognostic value of FFR improvement after PCI (Δ FFR) on patients' symptoms and 2-year outcomes in a post hoc analysis of data from patients the FAME 1 and FAME 2 trials. Of 837 lesions (639 patients with pre- and post-PCI FFR), 277 were in the lowest tertile (Δ FFR >0.18), 282 in the middle tertile ($0.19 > \Delta$ FFR < 0.31), and 278 in the highest tertile (Δ FFR > 0.31) and vessel-oriented cardiac events were significantly more frequent in the lowest tertile ($n = 25$ of 277 [9.1%]) compared with the highest tertile ($n = 13$ of 278 [4.7%]; $P = .04$). In addition, a significant association was observed between Δ FFR and symptomatic relief ($P = .02$). Thus, the larger the improvement in FFR, the larger the symptomatic relief and the lower the event rate. Measuring FFR before and after PCI provides clinically useful prognostic data.

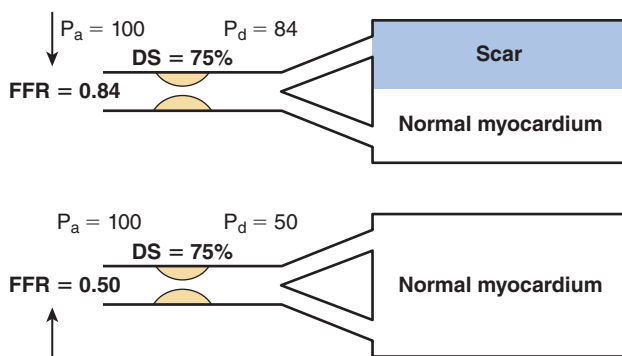
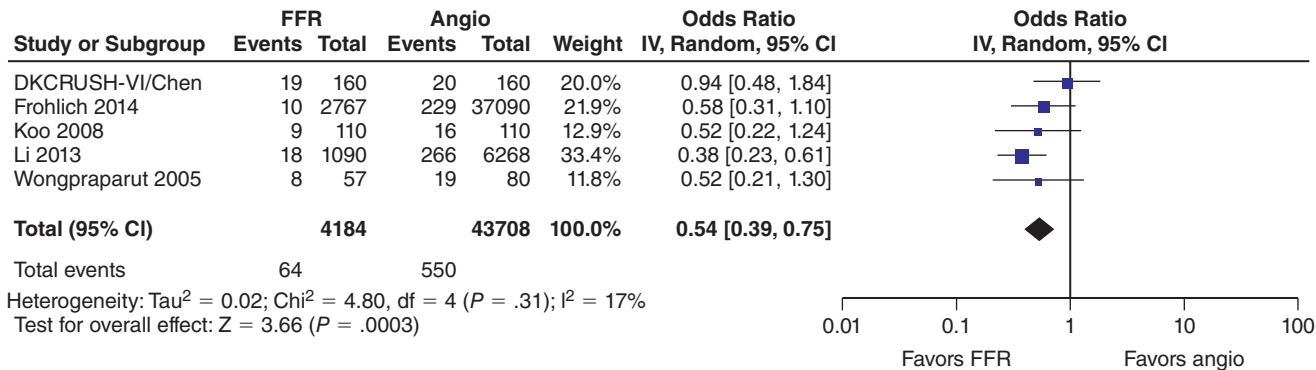
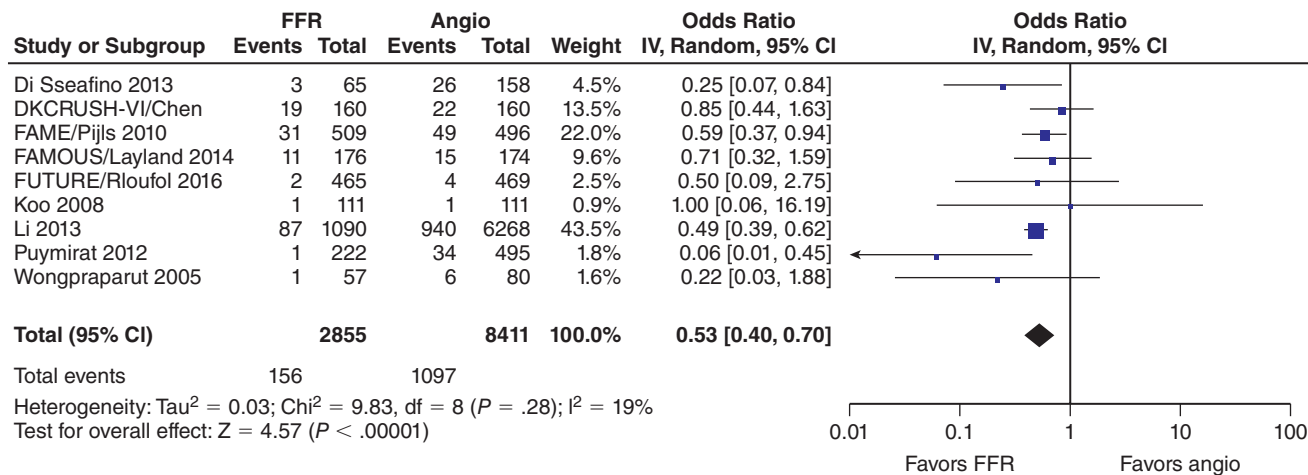


FIGURE 15.25 Illustration of myocardial bed size (and flow) on fractional flow reserve (FFR) value for fixed stenosis of 75% narrowing. *Top*, The myocardium is impaired or infarcted. The flow across the lesion is reduced yielding a high FFR of 0.84. *Bottom*, After the myocardium recovers, the flow increases and the FFR drops to 0.50. For this reason, in patients with acute coronary syndromes, the dynamic nature of the myocardial bed and lesion make target lesion FFR unreliable if negative. P_a , pressure in aorta; P_d , pressure distal to the stenosis.



A



B

FIGURE 15.26 The measure of effect of fractional flow reserve (FFR) on myocardial infarction (MI) in each study plotted using odds ratio (OR) and 95% confidence interval (CI) on a forest plot. The overall results showing lower MI in (i.e., favors) the FFR group during hospitalization (**A**) and at follow-up (**B**). (From Enezate T, Omran J, Al-Dadah AS, et al. Fractional flow reserve versus angiography guided percutaneous coronary intervention: an updated systematic review. *Catheter Cardiovasc Interv.* 2017;1-10.)

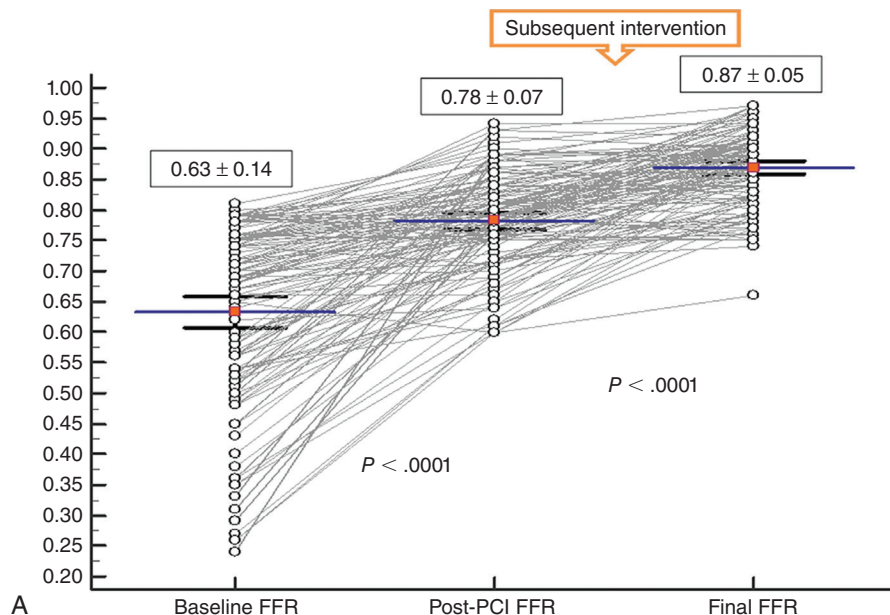


FIGURE 15.27A Impact of interventions on post-percutaneous coronary intervention (PCI) fractional flow reserve (FFR). Subsequent interventions undertaken to address suboptimal post-PCI FFR may result in persistently ischemic FFR despite angiographic optimal results necessitating subsequent intervention ($n = 137$ or 20% of all lesions). The FFR before reintervention was 0.78 ± 0.07 and after intervention was 0.87 ± 0.05 . Interventions attempting to raise the FFR included additional stenting, intravascular ultrasonography, optical coherence tomography, and postdilation of the stent. (From Agarwal SK, Kasula S, Hacıoglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing post-intervention fractional flow reserve to optimize acute results and the relationship to long-term outcomes. *JACC Cardiovasc Interv.* 2016;9(10):1022-1031. doi: 10.1016/j.jcin.2016.01.046)

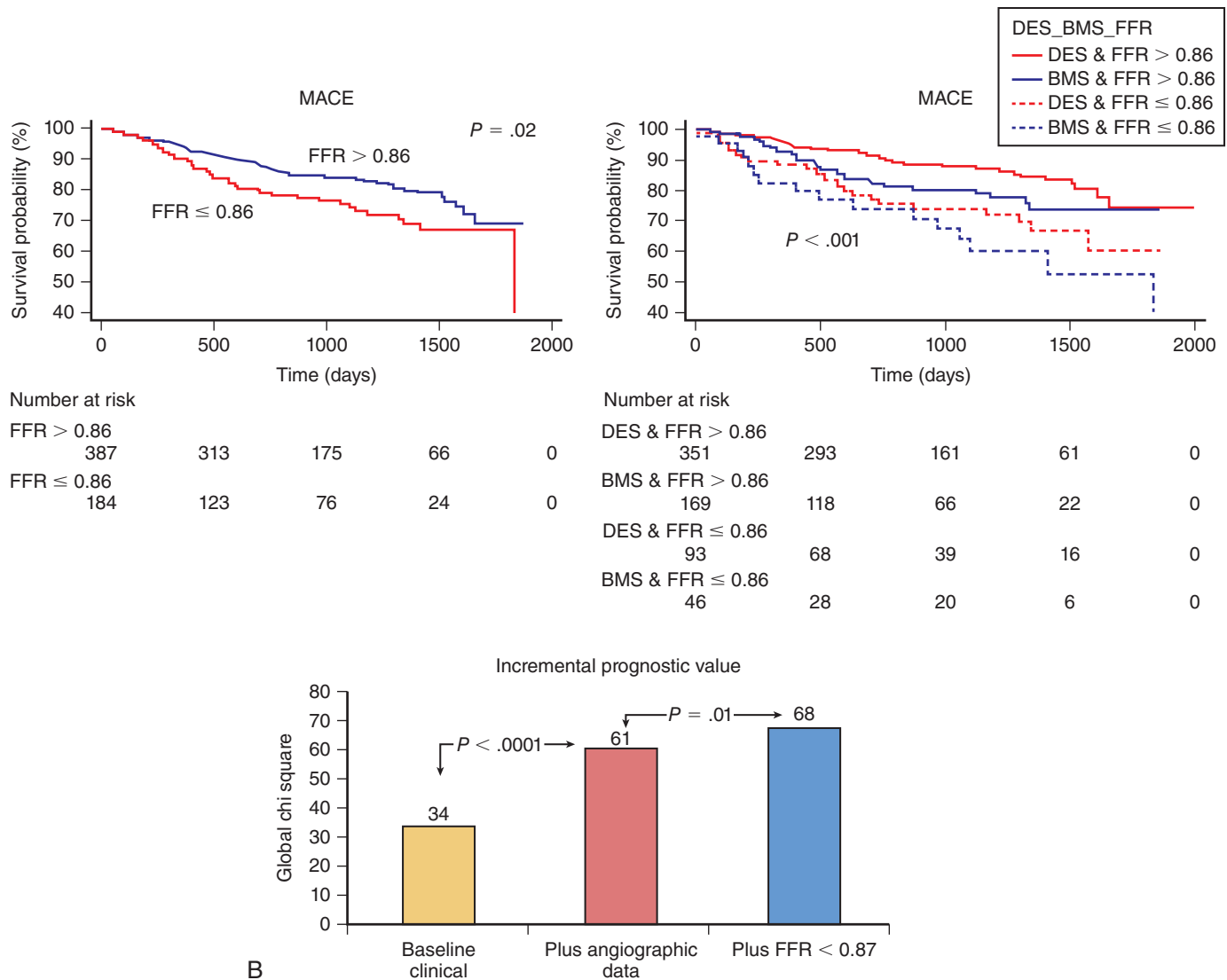


FIGURE 15.27B Prognostic value of post-percutaneous coronary intervention (PCI) fractional flow reserve (FFR). Top left, Kaplan-Meier curve showing significantly higher survival free of major adverse cardiovascular events (MACEs) in the patients with final FFR greater than 0.86 in comparison with the final FFR 0.86 or less group. Top right, Kaplan-Meier curve showing significantly higher survival free of MACE in the patients with drug-eluting stents (DES) and final FFR greater than 0.86 followed by patients with bare-metal stents (BMSs) and final FFR greater than 0.86 followed by patients with DES and final FFR 0.86 or less followed by patients with BMSs and final FFR 0.86 or less, respectively. Bottom, Incremental prognostic value of final FFR. The addition of final FFR less than 0.87 added incremental value for prediction of MACE over baseline clinical and angiographic data (all $P < .05$). DES drug eluting stent, BMS bare metal stent. (Adapted from Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. *JACC Cardiovasc Interv.* 2016;9(10):1022-1031. doi:10.1016/j.jcin.2016.01.046; Hakeem A, Uretsky BF. Role of postintervention fractional flow reserve to improve procedural and clinical outcomes. *Circulation.* 2019;139:694-706.)

ASSESSING COLLATERAL FLOW

Used mostly for research, the assessment of the collateral circulation can be obtained and quantitated based on pressure or Doppler flow. The pressure-derived fractional collateral flow is defined as the mean coronary wedge pressure (distal coronary pressure during balloon occlusion) divided by the mean aortic pressure (if the central venous pressure is abnormal, then it should be subtracted from both the wedge and aortic pressures). In general, a pressure-derived FFR of 0.25 or more suggests sufficient collaterals to prevent ischemia during PCI. Furthermore, these patients have a significantly lower adverse event rate during follow-up than those with insufficient collaterals at the time of PCI (pressure-derived collateral flow <0.25). Pressure-derived collateral flow has also been

studied in patients with acute MI and has been shown to be the major determinant of left ventricular recovery after primary PCI. Unfortunately, this technique for assessing collaterals is limited by the requirement for coronary artery occlusion.³⁴

Contemporary interest in the collateral circulation now centers around the impact of revascularization in patients with chronic total coronary occlusions (CTOs). A vessel remote from a chronic total occlusion (CTO) may be impacted by the restored flow after CTO revascularization. The physiological assessment of both the donor and target vessel of CTO and shared collateral supply is complex. The initial assessment of a supply artery lesion may differ from the post-CTO setting in the degree of regression of collaterals, the assessment of the microcirculation, and the impact of collateral steal from the CTO bed. Recent

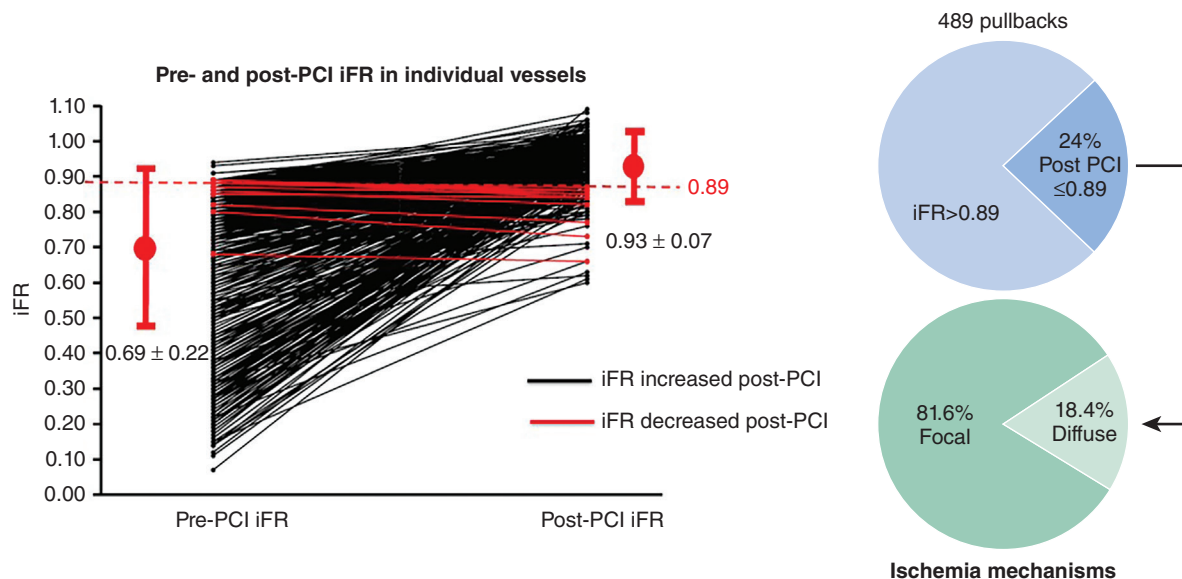


FIGURE 15.28 Post-percutaneous coronary intervention (PCI) physiology. The Define PCI study found a significant residual ischemia after angiographically successful PCI occurring in 24% of patients (*right panel, dark blue*). Most patients had residual pressure gradients caused by focal untreated narrowings and potentially amenable to treatment with additional PCI. Of note, post-PCI angiography poorly correlated with physiologic measures. *iFR*, Instantaneous wave-free ratio. (From Jeremias A, Davies JE, Maehara A, et al. Blinded physiological assessment of residual ischemia after successful angiographic percutaneous coronary intervention: the DEFINE PCI study. *J Am Coll Cardiol Interv*. 2019;12:1991-2001.)

studies have shown that a donor vessel stenosis FFR may change with the reduction of the supply zone after the CTO after recanalization. The physiological assessment of patients with a CTO is an area of interest for collateral flow studies.

INDEX OF MICROCIRCULATORY RESISTANCE

An impaired microcirculation carries an adverse prognosis. To study the microcirculation, Doppler coronary flow velocity reserve and thermodilution coronary flow are coupled with pressure to derive resistance indices. The index of microcirculatory resistance (IMR), defined as the ratio of distal coronary pressure to the inverse of the mean transit time during maximal hyperemia, has been reported to provide prognostic information for STEMI patients. IMR is a quantitative index that is unique to the microcirculation and independent of epicardial CAD.^{35,36} IMR is superior to CFR (Doppler CFR) because it is not affected by resting hemodynamics, making it more reproducible, even after hemodynamic perturbations. When measured immediately after primary PCI for STEMI, IMR predicts the amount of myocardial damage and left ventricular recovery better than other indices, such as CFR, ST-segment resolution, or TIMI myocardial perfusion grade, and is an independent predictor of long-term clinical outcomes, including death and rehospitalization for heart failure.³⁷ Examples of invasive measurements characterizing the microcirculation are shown in [Figures 15.29 to 15.31](#).

After primary angioplasty, Fearon et al.³⁵ found that patients with preserved IMR may have greater recovery of regional ventricular function after primary angioplasty for STEMI. In 253 patients, IMR was measured immediately after primary PCI using a pressure-temperature sensor wire. The

prognostic value of IMR was compared with CFR, TIMI myocardial perfusion grade, and clinical variables. The mean IMR was 40.3 ± 32.5 . Patients with an IMR greater than 40 had a higher rate of death or rehospitalization at 1 year than those with an IMR of 40 or less (17% vs 7%; $P = .027$). During follow-up (2.8 years), 14% experienced the primary endpoint, and 4% died. An IMR greater than 40 was associated with an increased risk of death or rehospitalization for heart failure (HR, 2.1; $P = .034$) and of death alone (HR, 3.95; $P = .028$). An IMR greater than 40 was the only independent predictor of death alone (HR, 4.3; $P = .02$; [Figure 15.32](#)). Like a low reference vessel coronary flow velocity reserve, an elevated IMR at the time of primary PCI predicts poor long-term outcomes. In addition to providing prognostic information in this important patient subset, IMR may potentially be used in selecting patients with relatively preserved postinfarct microvasculature who might most benefit from regional delivery of regenerative cell therapies.

SUMMARY AND FUTURE DIRECTIONS

The integration of coronary physiology with angiography has proven to be invaluable in aiding the physician with decision making in equivocal stenosis and multivessel disease. Through physiological assessment of coronary artery stenosis, FFR/NHPR identifies lesions with ischemic potential and essentially functions as a stress test in the catheterization laboratory.

Recommendations for adjunctive diagnostic tools have been provided in the 2011 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) guideline for PCI and the 2018 European Society of Cardiology (ESC) guideline. According to the ACC/AHA/SCAI guideline, FFR

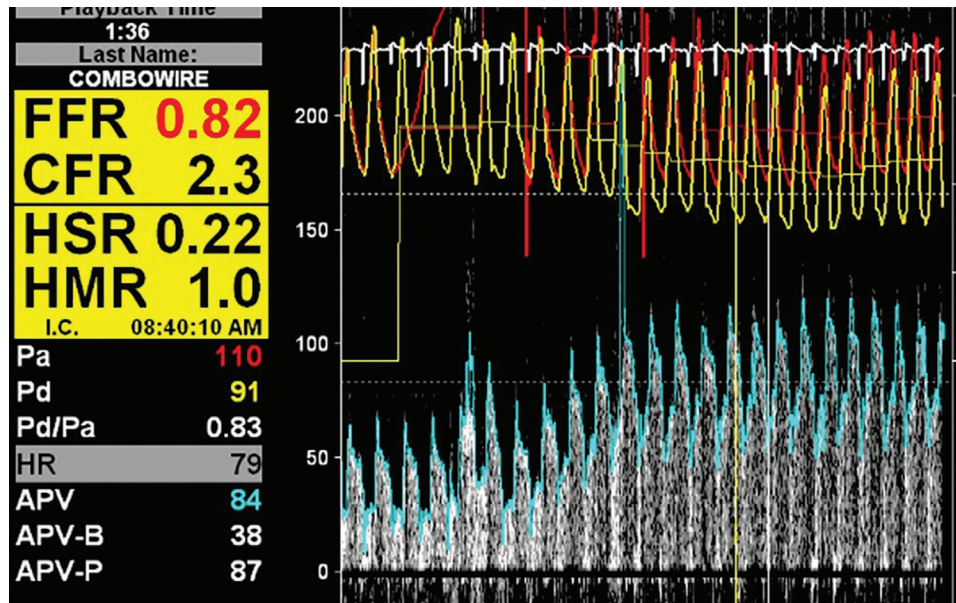


FIGURE 15.29 Simultaneous measurement of pressure and flow (by combination Doppler guidewire, Abbott Vascular). The *upper portion* of the figure shows (from top to bottom) the electrocardiography, arterial (P_a) and poststenotic wire pressures (P_d) at rest (*left side of the tracing*) and during hyperemia (*right side of the tracing*). The *lower portion* of the figure depicts the Doppler resting and hyperemic response. These signals are used to calculate the fractional flow reserve (FFR), coronary flow reserve (CFR), hyperemic stenosis resistance (HSR), and hyperemic microcirculatory resistance (HMR); other measurements include average peak velocity (APV) at baseline (B) and hyperemic flow velocity (P, peak). P_a , Pressure, aorta; P_d , Pressure, distal to stenosis.



FIGURE 15.30 Simultaneous measurement of pressure and flow (by thermodilution). The *upper portion* of the figure shows pressures proximal (P_a) and distal (P_d) at rest (*left*) and during hyperemia (*right*). The *lower portion* of the figure depicts the thermodilution curves at rest and during hyperemia (Hyp) with the associated average transit times at baseline and at hyperemia circled. These values are used to calculate the coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR), as seen on the *right side* of the panel. Hyperemic stenosis resistance index (HSRv) = $P_a - P_d/APV_{hyper}$. IMR = $P_a * Tmn [(P_d - P_w)/(P_a - P_w)]$. CFR, coronary flow velocity reserve; FFR, fractional flow reserve; HSR, hyperemic stenosis resistance. (From Martin KC, Yeung AC, Fearon WF. Invasive assessment of the coronary microcirculation. *Circulation*. 2006;113(17):2054-2061.)

is reasonable to assess angiographic intermediate coronary lesions (40%–70% diameter stenosis) and can be useful for guiding revascularization decisions in patients with SIHD (Class IIa, level of evidence A).

The more recent ESC guidelines give FFR and iFR a Class I level of evidence, a recommendation to assess the hemodynamic relevance of a stenosis when evidence of ischemia is not available. However, a correction to the 2017 multi society appropriate use criteria for PCI stated,

“Substitution of a newer coronary pressure ratio that does not require hyperemia for FFR (i.e., any NHPR noted above) may be considered provided the appropriate reference values are used.” The remarkable improvement in patient outcomes with implementation of this strategy supports the ischemia-guided revascularization strategy and is prompting a shift in the existing coronary revascularization paradigm. [Table 15.6](#) provides applications of FFR in current clinical practice.

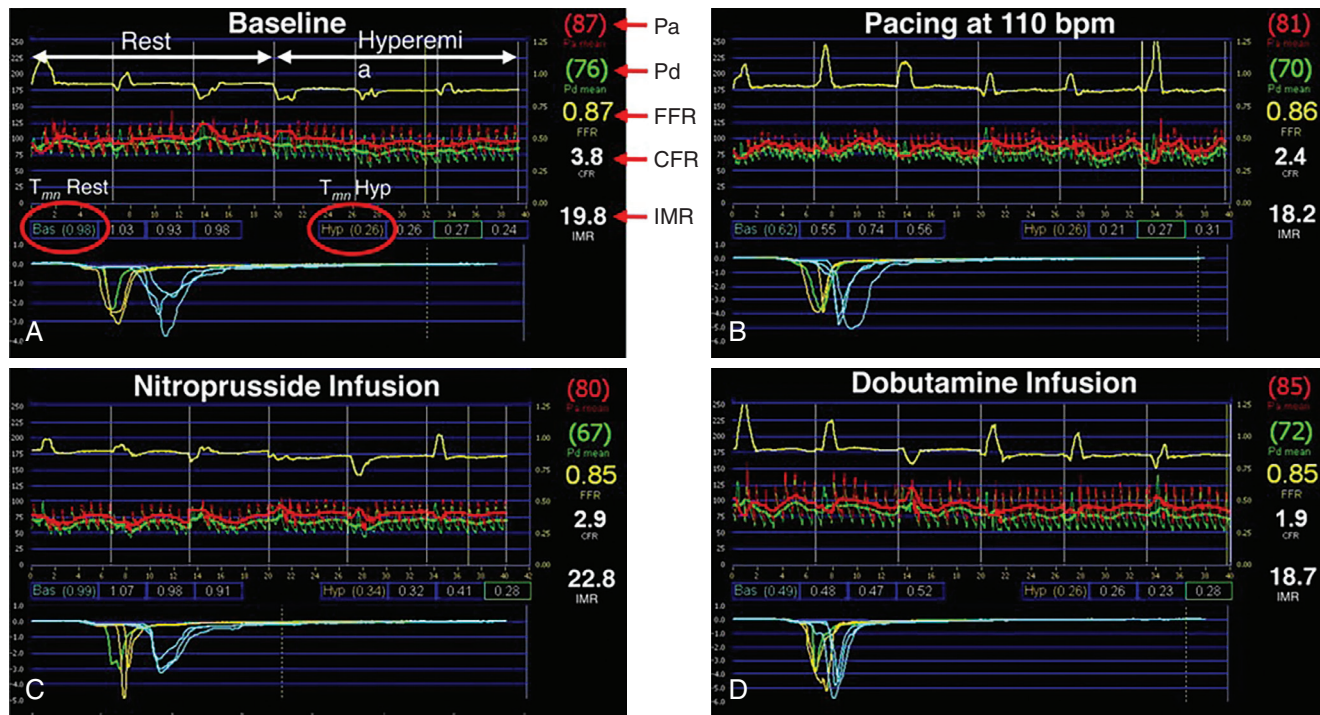


FIGURE 15.31 Hemodynamic dependence of coronary flow reserve (CFR), index of microcirculatory resistance (IMR), and fractional flow reserve (FFR). Representative hemodynamic recordings are shown for a single patient under the following hemodynamic conditions: baseline (A), right ventricular pacing at 110 beats/min (B), nitroprusside infusion (C), and dobutamine infusion (D). Each graph is divided into two windows; the upper window displays the pressure segments recorded during each thermodilution injection. The segments are separated from each other by white vertical lines. The upper window displays aortic (P_a) phasic and mean pressure in red and distal coronary (P_d) phasic and mean pressure in green. The lower graph displays the thermodilution injections (baseline injections in blue and hyperemic injections in orange). Between the two graphs are the mean T_{mn} values. To the right of each panel, the values of mean hyperemic P_a and P_d , FFR, CFR, and IMR are shown. *Hyp*, Hyperemic. (From Ng MK, Yeung AC, Fearon WF. Invasive assessment of the coronary microcirculation: superior reproducibility and less hemodynamic dependence of index of microcirculatory resistance as compared with coronary flow reserve. *Circulation*. 2006;113:2054-2061.)

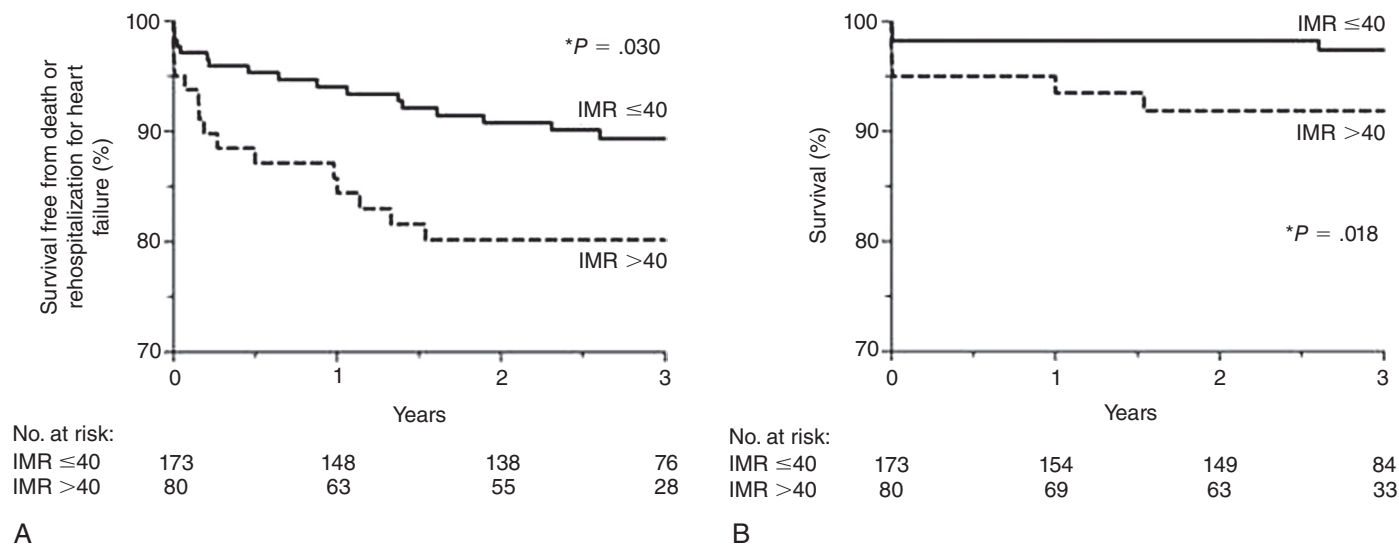


FIGURE 15.32 The index of microcirculatory resistance (IMR) less than 40 is associated with better survival free of death or rehospitalization for heart failure and survival free of death. **A**, Kaplan-Meier curves displaying the relationship between IMR greater than 40 and survival free of death or rehospitalization for heart failure. **B**, Kaplan-Meier curves displaying the relationship between IMR greater than 40 and survival free of death. (From Fearon WF, Low AF, Yong AS, et al. Prognostic value of the index of microcirculatory resistance measured after primary percutaneous coronary intervention. *Circulation*. 2013;127:2436-2441.)

TABLE 15.6 Applications of Coronary Physiologic Measurements in the Catheterization Laboratory

Before Intervention
• Establish hemodynamic significance of angiographically intermediate lesions. • Assess diffuse disease. • Evaluate ostia and bifurcation lesions. • Guide therapy with tandem lesions. • Assess culprit and nonculprit lesion in multivessel CAD or ACS. • Assess collateral circulation.
After Intervention
• Estimate prognosis with post-PCI FFR or NHPR. • Assess for residual lesions or diffuse disease not amenable to stenting. (Stent optimization is anatomically determined.)
In the Setting of Nonobstructive Disease
• Assess for structural changes in the microcirculation. • Assess for vasomotor disorders.

ACS, Acute coronary syndrome; CAD, coronary artery disease; FFR, fractional flow reserve; NHPR, nonhyperemic pressure ratio; PCI, percutaneous coronary intervention.

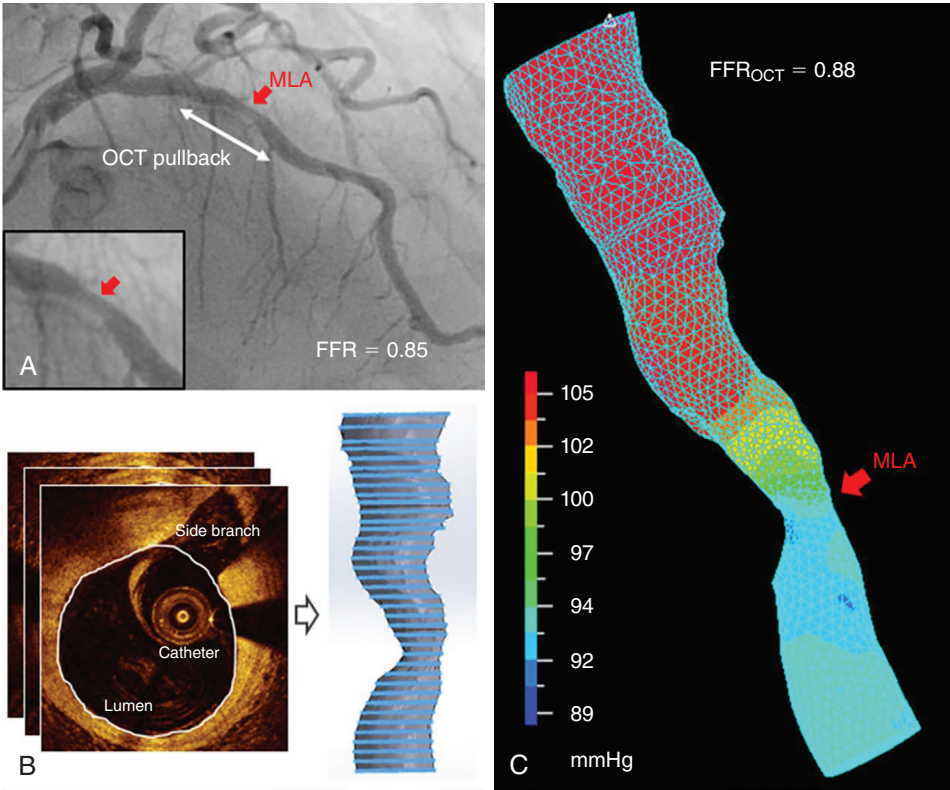


FIGURE 15.33 Computational flow dynamics (CFD) model and fractional flow reserve (FFR) simulation. **A**, Coronary angiography of the left anterior descending artery. **B**, Optical coherence tomography (OCT) lumen-derived three-dimensional (3D) geometry. **C**, CFD computation to obtain FFR. The 3D coronary geometry was constructed from a series of OCT cross-sectional lumen contours using 3D computer-aided design software. Numeric simulation of blood flow was then performed after the volume mesh was generated. *MLA*, Minimal lumen area. (From Ha J, Kim JS, Lim J, et al. Assessing computational fractional flow reserve from optical coherence tomography in patients with intermediate coronary stenosis in the left anterior descending artery. *Circ Cardiovasc Interv*. 2016;9(8):e003613.)

THE FUTURE OF INTRACORONARY PHYSIOLOGY: ANGIOGRAPHICALLY DERIVED FRACTIONAL FLOW RESERVE

The future of catheterization laboratory-based translesional physiology will likely be augmented by angiographically derived FFR computations. Currently, angiographic systems are available to compute FFR from 3D-reconstructed angiograms using computational fluid dynamics with

high accuracy with invasive FFR of around 80%.³⁸ Computational flow dynamics model and FFR simulation have also been applied to optical coherence tomography (OCT) (Figure 15.33) lumen-derived 3D geometry. The 3D coronary geometry was constructed from a series of OCT cross-sectional lumen contours using 3D computer-aided design software. Numeric simulation of blood flow was then performed after the volume mesh was generated.³⁹

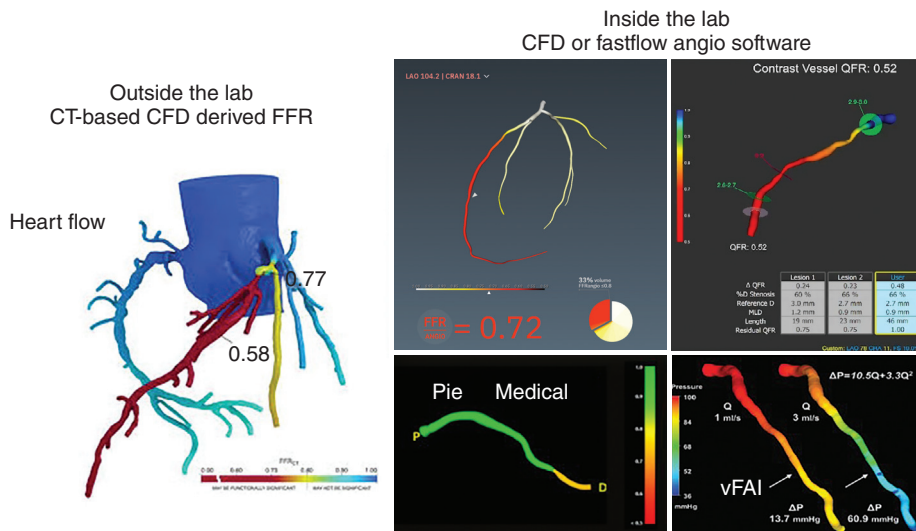


FIGURE 15.34 Methodologies for angiographically derived fractional flow reserve (FFR). *Upper left*, CathWorks FFRangio® Systems. *Upper right*, Medis quantitative flow ratio (QFR). *Lower left*, Pie medical. *Lower right*, Virtual functional assessment index (vFAI). *CFD*, Computational flow dynamics; *CT*, computed tomography. (From Papafakis MI, Muramatsu T, Ishibashi Y, et al. Fast virtual functional assessment of intermediate coronary lesions using routine angiographic data and blood flow simulation in humans: comparison with pressure wire - fractional flow reserve. *EuroIntervention*. 2014;10(5):574-583. doi:10.4244/EIJY14M07_01.)

Continued research and clinical studies for the application and validation of angiographically derived FFR based on various technical assumptions of flow rates myocardial mass and resistance are ongoing for both CT-derived and angiography-derived images (e.g., quantitative flow ratio) to assess for hemodynamic significance of lesions without wires (Figure 15.34)

REFERENCES

1. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation*. 1995;92(8):2333-2342.
2. Johnson NP, Kirkeeide RL, Gould KL. History and development of coronary flow reserve and fractional flow reserve for clinical applications. *Intervent Cardiol Clin*. 2015;4:397-410.
3. Toth G, Hamilos M, Pyxaras S, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J*. 2014;35(40):2831-2838.
4. Johnson NP, Tóth GG, Lai D, et al. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol*. 2014;64(16):1641-1654.
5. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334:1703-1708.
6. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation*. 1993;87(4):1354-1367.
7. Toth GG, De Bruyne B, Rusinaru D, et al. Impact of right atrial pressure on fractional flow reserve measurements: comparison of fractional flow reserve and myocardial fractional flow reserve in 1,600 coronary stenoses. *JACC Cardiovasc Interv*. 2016;9(5):453-459.
8. Johnson NP, Jeremias A, Zimmermann FM, et al. Continuum of vasodilator stress from rest to contrast medium to adenosine hyperemia for fractional flow reserve assessment. *JACC Cardiovasc Interv*. 2016;9(8):757-767.
9. Leone AM, Scalone G, De Maria GL, et al. Efficacy of contrast medium induced Pd/Pa ratio in predicting functional significance of intermediate coronary artery stenosis assessed by fractional flow reserve: insights from the RINASCI study. *EuroIntervention*. 2015;11:421-427.
10. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol*. 2012;59:1392-1402.
11. De Bruyne B, Oldroyd KG, Pijls NHJ. Microvascular (dys)function and clinical outcome in stable coronary disease. *J Am Coll Cardiol*. 2016;67(10):1170-1172.
12. Iqbal MB, Shah N, Khan M, et al. Reduction in myocardial perfusion territory and its effect on the physiological severity of a coronary stenosis. *Circ Cardiovasc Interv*. 2010;3:89-90.
13. Salcedo J, Kern MJ. Effects of caffeine and theophylline on coronary hyperemia induced by adenosine or dipyridamole. *Cathet Cardiovasc Interv*. 2009;74:598-605.
14. De Rosa S, Polimeni A, Petraro R, Davies JE, Indolfi C. Diagnostic performance of the instantaneous wave-free ratio. *Circ Cardiovasc Interv*. 2018;11(1):e004613.
15. Warisawa T, Cook CM, Howard JP, et al. Physiological pattern of disease assessed by pressure-wire pullback has an influence on fractional flow reserve/instantaneous wave-free ratio discordance. *Circ Cardiovasc Interv*. 2019;12(5):e007494.
16. Cook CM, Jeremias A, Petraro R, et al. Fractional flow reserve/instantaneous wave-free ratio discordance in angiographically intermediate coronary stenoses: an analysis using doppler-derived coronary flow measurements. *JACC Cardiovasc Interv*. 2017;10(24):2514-2524.
17. Kogame N, Ono M, Kawashima H, et al. The impact of coronary physiology on contemporary clinical decision making. *J Am Coll Cardiol Intv*. 2020;13:1617-1638.
18. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213-224.
19. Davies JE, Sen S, Dehbi HM, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med*. 2017;376(19):1824-1834.
20. Götzberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med*. 2017;376:1813-1823.
21. Hamilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation*. 2009;120:1505-1512.
22. Warisawa T, Cook CM, Rajkumar C, et al. Safety of revascularization deferral of left main stenosis based on instantaneous wave-free ratio evaluation. *JACC Cardiovasc Interv*. 2020;13(14):1655-1664.
23. Fearon WF, Yong AS, Lenders G, et al. The impact of downstream coronary stenosis on fractional flow reserve assessment of intermediate left main coronary artery disease: human validation. *J Am Coll Cardiol Intv*. 2015;8(3):398-403.
24. Pijls NH, De Bruyne B, Bech GJ, et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. *Circulation*. 2000;102:2371-2377.
25. Kikuta Y, Cook CM, Sharp ASP, et al. Pre-angioplasty instantaneous wave-free ratio pullback predicts hemodynamic outcome in humans with coronary artery disease: primary results of the international multicenter iFR GRADIENT registry. *J Am Coll Cardiol Intv*. 2018;11:757-767.
26. Shin D, Dai N, Lee JM, et al. Physiologic distribution and local severity of coronary artery disease and outcomes after percutaneous coronary interventions. *JACC Interv*. 2021;14(16):1771-1785.
27. Collet C, Sonck J, Vandelooy B, et al. Measurement of hyperemic pullback pressure gradients to characterize patterns of coronary atherosclerosis. *J Am Coll Cardiol*. 2019;74:1772-1784.
28. Engström T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomized controlled trial. *Lancet*. 2015;386(9994):665-671.

29. Layland J, Oldroyd KG, Curzen N, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. *Eur Heart J*. 2015;36(2):100-111.
30. Smits P, Abdel-Wahab M, Neumann FJ, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med*. 2017;376:1234-1244.
31. Hakeem A, Uretsky BF. Role of postintervention fractional flow reserve to improve procedural and clinical outcomes. *Circulation*. 2019;139:694-706.
32. Jeremias A, Davies JE, Maehara A, et al. Blinded physiological assessment of residual ischemia after successful angiographic percutaneous coronary intervention: the DEFINE PCI study. *J Am Coll Cardiol Interv*. 2019;12:1991-2001.
33. Fournier S, Ciccarelli G, Toth GG, et al. Association of improvement in fractional flow reserve with outcomes, including symptomatic relief, after percutaneous coronary intervention. *JAMA Cardiol*. 2019;4(4):370-374.
34. Pijls NH, Bech GJ, El Gamal MI, et al. Quantification of recruitable coronary collateral blood flow in conscious humans and its potential to predict future ischemic events. *J Am Coll Cardiol*. 1995;25:1522-1528.
35. Fearon WF, Low AF, Yong AC, et al. Prognostic value of the index of microcirculatory resistance measured after primary percutaneous coronary intervention. *Circulation*. 2013;127(24):2436-2441.
36. Ng MK, Yeung AC, Fearon WF. Invasive assessment of the coronary microcirculation: superior reproducibility and less hemodynamic dependence of index of microcirculatory resistance as compared with coronary flow reserve. *Circulation*. 2006;113:2054-2061.
37. Seiler C, Fleisch M, Billinger M, et al. Simultaneous intracoronary velocity- and pressure-derived assessment of adenosine-induced collateral hemodynamics in patients with one- to two-vessel coronary artery disease. *J Am Coll Cardiol*. 1999;34:1985-1994.
38. Ramasamy A, Jin C, Tufaro V, et al. Computerized methodologies for non-invasive angiography-derived fractional flow reserve assessment: a critical review. *J Interv Cardiol*. 2020;2020:6381637.
39. Ha J, Kim JS, Lim J, et al. Assessing computational fractional flow reserve from optical coherence tomography in patients with intermediate coronary stenosis in the left anterior descending artery. *Circ Cardiovasc Interv*. 2016;9(8):e003613.



16

Intravascular Ultrasound Imaging

KHALED M. ZIADA

BACKGROUND AND LIMITATIONS OF ANGIOGRAPHY, 290

INTRAVASCULAR ULTRASOUND IMAGING: BASIC IMAGE AND MEASUREMENTS, 292

GUIDELINES FOR USE AND APPROPRIATE INDICATIONS, 295

DIAGNOSTIC APPLICATIONS, 295

Ambiguous Angiograms and Intermediate Coronary Lesions, 295

Evaluation of Left Main Coronary Artery Indeterminate Lesions, 297

Evaluation of Transplant Vasculopathy, 299

INTERVENTIONAL APPLICATIONS, 299

Selection of Intermediate Lesions for Intervention, 300

Vessel Sizing and Lesion Preparation, 300
Intravascular Ultrasound Imaging in Coronary Stenting, 300

Optimal Intravascular Ultrasound-Guided Stenting and Clinical Outcomes, 305

Management of Stent Restenosis, 306

Assessment of Complications After Intervention, 307

Advanced Applications of Intravascular Ultrasound Imaging in Chronic Total Occlusion Angioplasty, 309

INTRAVASCULAR ULTRASOUND IMAGING IN THE PERIPHERAL ARTERIAL SYSTEM, 310

RESEARCH APPLICATIONS: PROGRESSION AND REGRESSION TRIALS, 311

ADVANCING INTRAVASCULAR ULTRASOUND TECHNOLOGIES AND FUTURE DIRECTIONS, 312

Intravascular Ultrasound-Derived Virtual Histology, 312

Intravascular Ultrasound and Near-Infrared Spectroscopy, 313

High-Definition Imaging, 314

Intravascular Ultrasound and Optical Coherence Tomography Imaging, 314

ACKNOWLEDGMENT, 315

BACKGROUND AND LIMITATIONS OF ANGIOGRAPHY

Contrast angiography has been the gold standard of coronary artery imaging for more than 6 decades. However, it is important to understand that angiograms only delineate the coronary lumen with no direct imaging or examination of the arterial wall. With the growing interest in vascular biology and understanding of the structure and topography of the atherosclerotic plaque, intravascular ultrasound (IVUS) imaging fills a gap in our understanding of coronary disease because it allows in vivo examination of both the arterial wall and the lumen of the coronary arteries with high resolution. Although newer intravascular imaging modalities have evolved in the past decade, IVUS imaging remains the most mature adjunctive imaging modality and is the one technique with a large body of literature to support its application.

Conceptually, it is easy to understand how angiography of the coronary arteries may not be the perfect imaging modality. The coronary arteries are constantly moving structures with complex, three-dimensional (3D) lumen shapes and atherosclerotic lesions of various distributions and compositions that need to be depicted on a two-dimensional display. Therefore, it is critically important for the angiographer to understand the limitations of the technique. This will allow a more realistic processing of the information, which is necessary when making diagnoses and in clinical decision making.^{1,2} One of the most basic limitations is that fluoroscopy and cine angiography have limited resolution that is not adequate to delineate all the information needed from a coronary angiogram, even with near-universal adoption of digital imaging and flat-panel technology. Because of these complexities and limitations, interpretation of coronary angiograms has traditionally been riddled by marked inter- and intraobserver variability.^{3,4}

As stated and because angiograms are essentially contrast silhouettes of the lumen, it is not possible to directly discern whether the arterial wall is thickened (i.e., diseased) or not. This is inferred by a reduction in the diameter of the lumenogram in one segment compared with an adjacent one. Thus, the segmental construct in interpretation of angiograms is based on the assumption that narrower segments are the sites of disease, and adjacent larger segments represent the normal size of the artery or at least of its lumen. Yet autopsy studies have consistently demonstrated that atherosclerosis is diffuse, affecting almost all segments of an artery, albeit with varying severity.^{5,6} Therefore, the “focal” lesions frequently described on angiography are the more diseased sites, but the “normal” or “mildly irregular” segments are almost always diseased as well. This leads to the angiographic underestimation of disease severity and degree of narrowing at the worst lesion sites (Figure 16.1).

Arterial remodeling, first described by Glagov et al.,⁷ is another important phenomenon that can significantly affect angiographic interpretation. Arterial remodeling is the outward displacement of the arterial wall with increasing plaque size. This compensatory enlargement allows the artery to accommodate a certain amount of plaque volume without affecting the size of the lumen. Stenoses develop only when this mechanism is overwhelmed by increasing plaque size. Therefore, by definition, interpretation of contrast lumenograms based on differences in lumen size from one segment to the other is not helpful in recognizing early “well-compensated” stages of disease. Remodeled arterial segments with significant plaque burden can thus be described as “angiographically normal.”

Another phenomenon, “negative remodeling,” can also contribute to development of luminal narrowing in

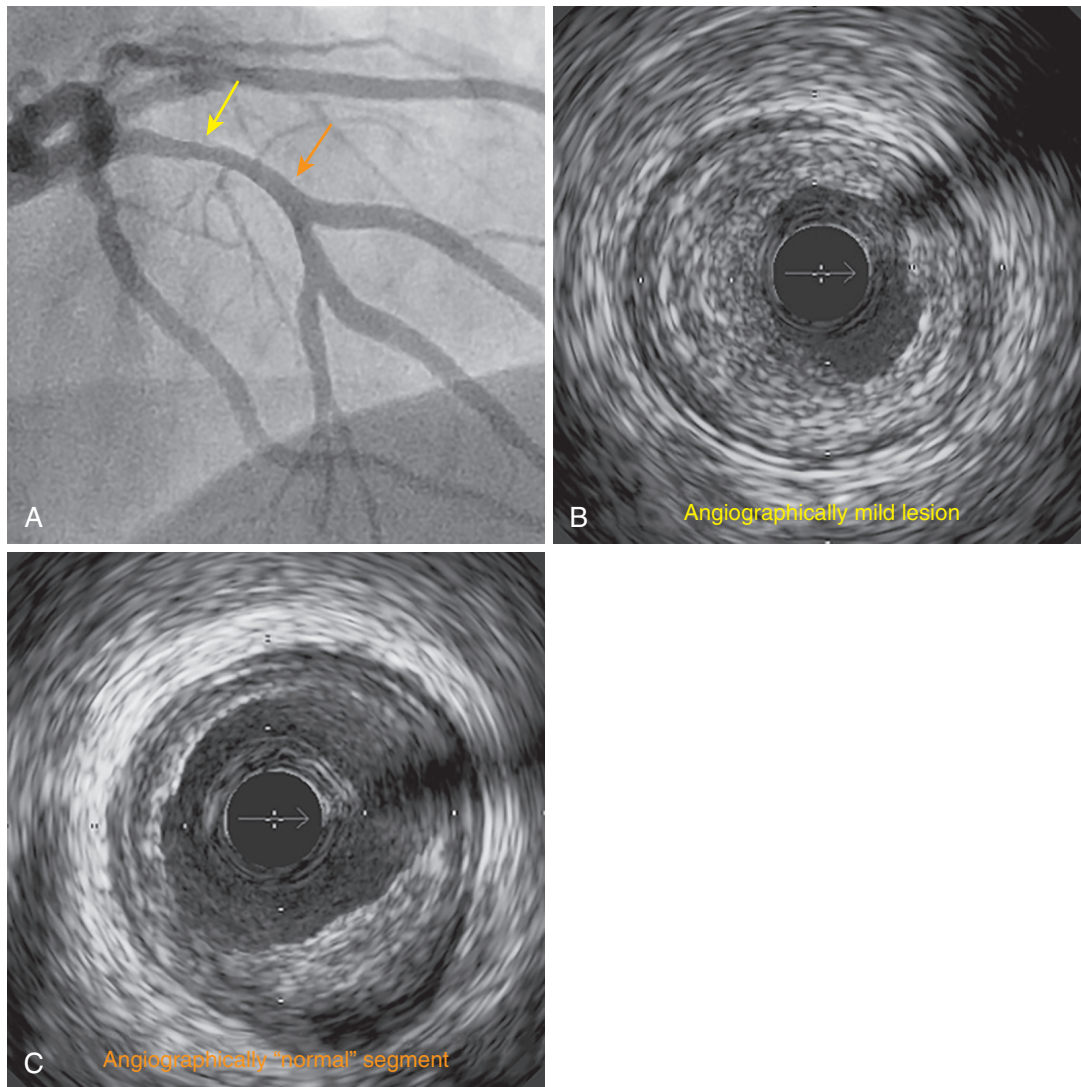


FIGURE 16.1 Angiographic underestimation of disease severity. A cranial angiographic projection of the left anterior descending coronary artery (A). There is a proximal segment narrowing (yellow arrow) that appears mild to moderate in severity compared with the apparently “normal” proximal-mid segment (orange arrow). Intravascular ultrasound imaging reveals a severe stenosis at the site of the proximal stenosis (B), with a lumen area of less than 3.5 mm² and cross-sectional narrowing greater than 70%. The angiographic underestimation is caused by the diffuse nature of disease involving the apparently “normal” segment distal to the lesion. Imaging of this segment reveals moderate stenosis and plaque burden with an eccentric distribution (C).

a reverse manner. In these cases, the reduction in the size of the artery itself contributes more to the reduction in lumen size than what the size of the plaque would indicate. (Figure 16.2).⁸ The remodeling index is a metric relating the size of the artery at the lesion site to that at the proximal reference segment. An index exceeding 1.0 indicates compensatory enlargement at the lesion site, and a value less than 1.0 indicates shrinkage or negative remodeling (Figure 16.3). There is some evidence that positive remodeling is associated with acute presentations, but negative remodeling is more commonly seen in patients with stable angina.⁹

The complexity of coronary anatomy is another factor that limits the accuracy of angiographic depiction. The constantly moving tortuous arteries give off branches in different planes in a 3D space. The lesions may be eccentric in distribution, at bifurcation points, ostial in location, calcified, or have complex luminal topography. It takes

perfect orthogonal angiographic projections to delineate accurate information about one or more of these findings. Given that projections are frequently selected arbitrarily, it is maybe difficult for angiographers to visualize the lesion, define percent stenosis, and proceed with a management decision (Figures 16.4 and 16.5).^{1,2}

Contemporary well-trained angiographers should be able to use adjunctive technologies that can resolve the clinical dilemmas caused by limitations of angiography and reach accurate conclusions. Currently, the most commonly used technologies in the cardiac catheterization laboratory are IVUS, optical coherence tomography (OCT) imaging, fractional flow reserve (FFR), and instantaneous wave-free flow reserve (iFR) measurement. Whereas IVUS and OCT imaging address the limitations of angiography related to resolution and complexities of disease severity and distribution, FFR and iFR measurements address the discrepancy between the anatomic and functional significance of coronary lesions.

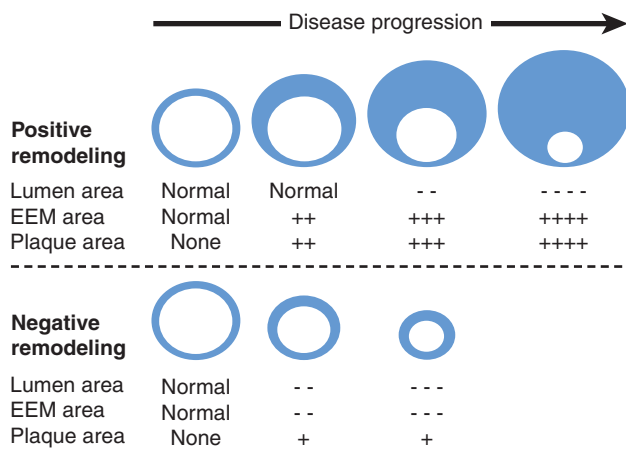


FIGURE 16.2 Arterial remodeling and disease progression. Schematic depiction of arterial remodeling in response to disease progression. In positive remodeling (*top*), early plaque accumulation in the arterial wall is associated with compensatory enlargement of vessel size. This allows plaque accumulation without compromise of lumen size. With disease progression, plaque deposition continues and can no longer be accommodated within the arterial wall, eventually leading to lumen compromise. In negative remodeling (*bottom*), the driver of luminal narrowing is not accumulating plaque as much as “shrinkage” of the artery size. The origins of the negative remodeling process and whether it is related to positive remodeling remain unclear. EEM, External elastic membrane (outer boundary of the arterial wall).

INTRAVASCULAR ULTRASOUND IMAGING: BASIC IMAGE AND MEASUREMENTS

Imaging is performed using a miniaturized ultrasound transducer placed on the tip of an imaging catheter and advanced into the lumen of the interrogated vessel. Contemporary imaging catheters are 3 to 3.5 Fr in diameter and can be used within 5- or 6-Fr guiding catheters. Coronary imaging catheters are typically advanced over standard angioplasty guidewires, 0.014 inch in diameter. By emitting and receiving reflected ultrasound beams, sector images can then be generated. Two different technologic approaches are used to generate a circumferential tomographic image of the entire cross-section of the vessel: (1) mechanical systems in which the transducer is composed of a single large piezoelectric crystal that is rotated at high speed to acquire images from all sectors of the circumference and (2) phased-array systems in which transducers are made of multiple small crystals that are sequentially activated to image adjacent sectors of the arterial cross-section. The imaging frequencies are 40 to 60 MHz for the mechanical systems and 20 MHz for the phased-array system. In both cases, the reflected ultrasound waveforms are processed into grayscale images, and the sectors are

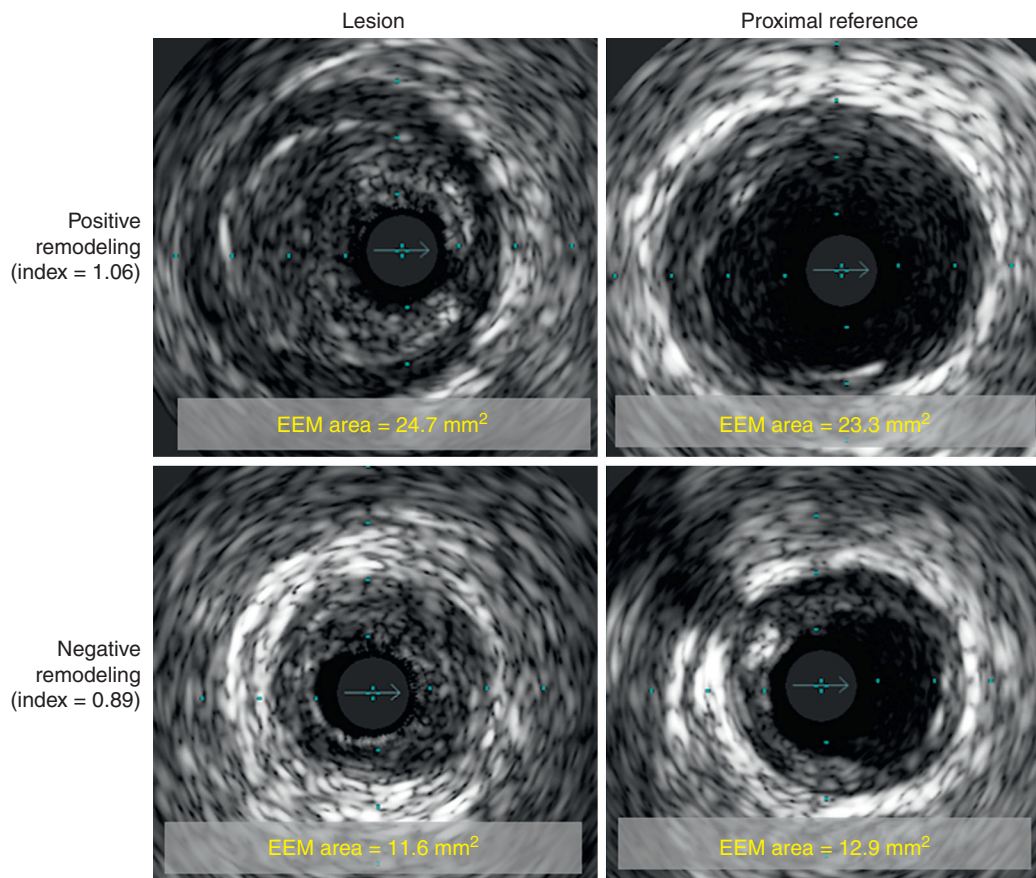


FIGURE 16.3 Intravascular ultrasound examples of coronary arterial remodeling. The remodeling index is calculated by dividing the external elastic membrane (EEM) area at the lesion site by that of the proximal reference segment. *Top*, ultrasound images from patient with unstable clinical presentation obtained at the lesion and proximal reference sites. The lesion shows positive remodeling with a remodeling index of 1.06. *Bottom*, ultrasound images from patient with chronic stable angina. The lesion shows negative remodeling with an index of 0.89.

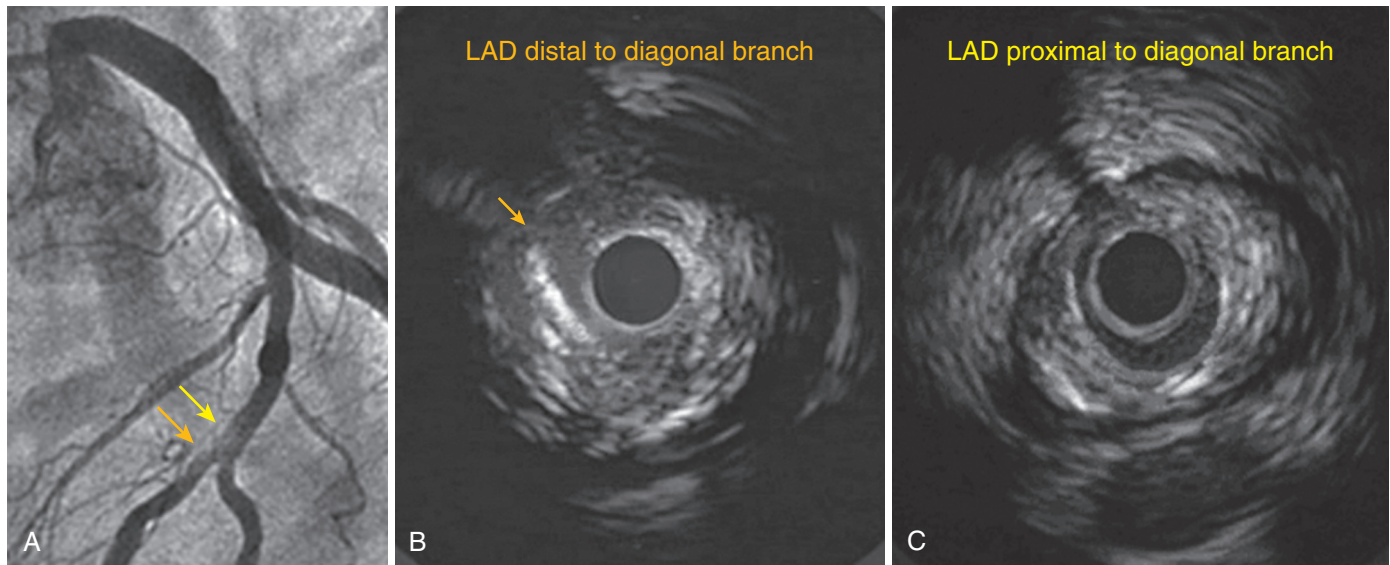


FIGURE 16.4 Role of intravascular ultrasound (IVUS) in ambiguous coronary angiograms. An angiogram of the left anterior descending artery reveals mild narrowing but significant haziness in the mid segment opposite the origin of the main diagonal branch (**A**). IVUS imaging is performed in the mid left anterior descending coronary artery (LAD) with special attention to the haziness distal and proximal to the bifurcation (orange and yellow arrows, respectively). Distal to the diagonal branch (**B**), there is severe concentric disease with eccentric dense plaque and evidence of plaque disruption (arrow). Proximal to the diagonal branch (**C**), there is concentric plaque with severe luminal narrowing. The plaque disruption, the distribution of plaque and the severity of disease around the bifurcation contribute to the haziness and result in angiographic underestimation of disease severity.

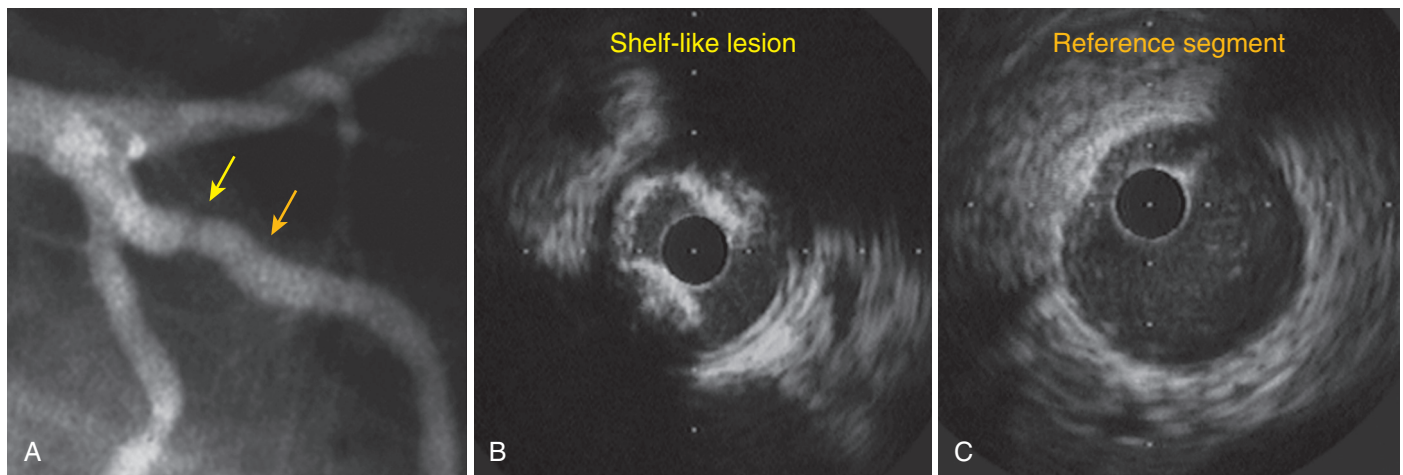


FIGURE 16.5 Role of intravascular ultrasound (IVUS) in ambiguous coronary angiograms. A left coronary angiogram reveals a shelf like lesion in a large mildly tortuous marginal branch of the circumflex (left). Despite multiple projections, the lesion severity cannot be well defined. IVUS imaging at the lesion site (yellow arrow) reveals a severe eccentric heavily calcified plaque (**B**). The lesion is very focal, such that the reference segment (orange arrow) is near normal on the IVUS pullback (right panel). The calcification, eccentricity, tortuosity, and very short lesion length contributed to the indeterminate angiographic appearance.

reconstructed into the full tomographic cross section of the artery.

Definitions and methodology of acquiring IVUS images and measurements are outlined in expert consensus documents on the standards of IVUS imaging from the American College of Cardiology, the European Society of Cardiology and more recently, the Japanese Association of Cardiovascular Interventions and Therapeutics.¹⁰⁻¹² Tomographic images obtained by the IVUS transducer show the reflection of the intima as an echodense layer followed by the media as an echolucent stripe. The adventitia is the outer echodense layer that represents the outer boundary of the artery and the adherent connective tissue and gives the arterial wall a

trilaminar appearance. Less commonly, and especially in very young individuals, the intima is so thin ($<300\ \mu\text{m}$ in thickness) that it leads to signal dropout and the traditional trilaminar appearance is replaced by a monolayer (Figure 16.6). Intimal thickening is the hallmark of arterial wall disease. When the intima thickens, it becomes more echodense and easier to visualize on display.

The basis IVUS measurements performed on a coronary artery image are shown in Figure 16.7. The echodense intimal leading edge defines the boundaries of the lumen, and the leading edge of the adventitia (the external elastic membrane [EEM]) defines the vessel area. The area between both tracings represents the plaque plus media or atheroma

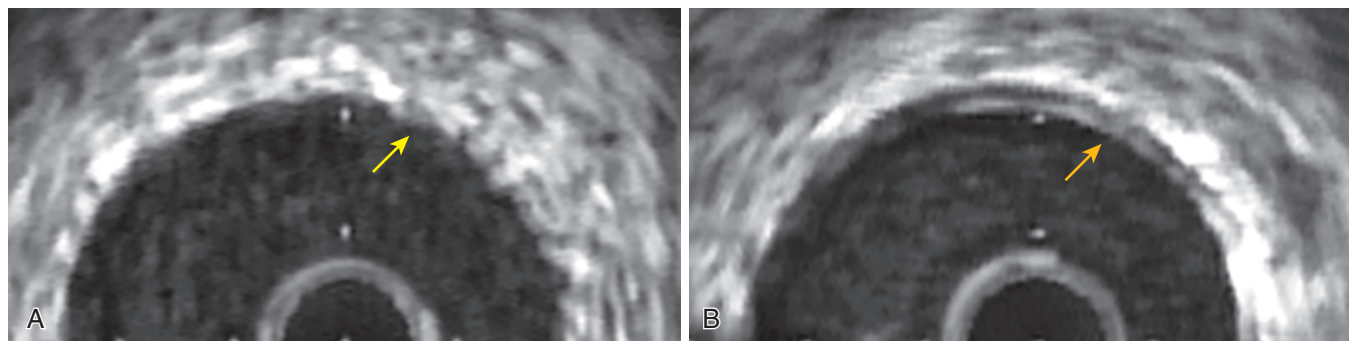


FIGURE 16.6 Intravascular ultrasound (IVUS) images of normal coronary arteries. The thickness of the normal intima is less than resolution of coronary IVUS catheter and thus it may not be visualized. In such a case, the only echodense layer is the adventitia, which leads to a monolayer appearance (yellow arrow, **A**). More frequently, the intima is mildly thickened, so it reflects ultrasound signals and can be seen as a leading echodense border (orange arrow, **B**). This gives the traditional trilaminar appearance of the normal or near-normal coronary arterial wall.

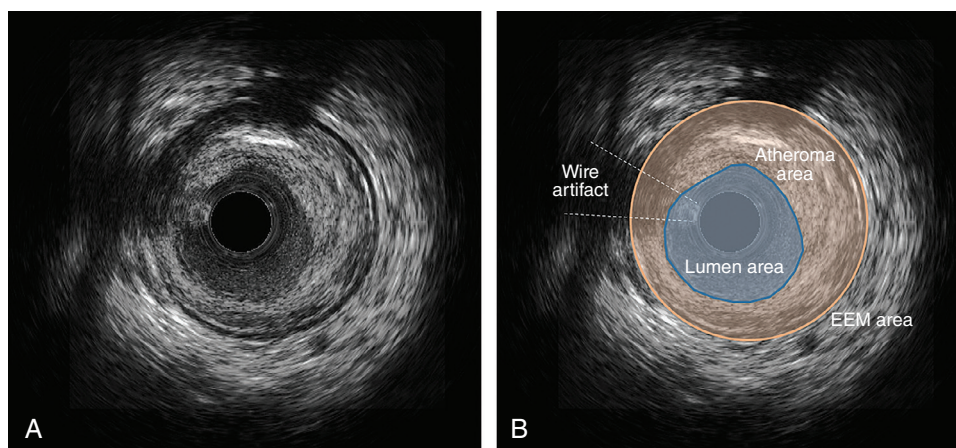


FIGURE 16.7 Basic intravascular ultrasound (IVUS) measurements on still frames. A typical IVUS image from a patient with coronary artery disease reveals evidence of intimal thickening and some degree of luminal narrowing. A representative image is shown here. The same image is shown in **A** and **B**, with the electronic tracings of the intimal leading edge and the external elastic membrane (EEM) superimposed on **B**. The tracings form the boundaries of the lumen and vessel, respectively. Areas and diameters are often measured using automated software. The area between the lumen and EEM boundaries represents the atheroma or plaque area. Expressing the plaque area as a percentage of the EEM area is usually referred to as cross-sectional narrowing, area stenosis, or plaque burden. The angioplasty wire casts a wedge-shaped shadow that prohibits ultrasound beams and hence appears echolucent or dark.

area. Lumen and vessel diameters can be measured as well. Plaque or atheroma area can be normalized to the size of the vessel by calculating a percent cross-sectional narrowing or plaque burden (plaque area / vessel area) $\times$ 100.

The IVUS catheter can be mounted on an automatic pull-back device that moves it along the arterial segment at a known and constant velocity (0.5 or 1.0 cm/s), thus allowing calculation of the length of the segment. Lumen and plaque areas, in addition to length, can then be used to calculate lumen and plaque volume. These are typically more accurate measures of disease burden and are commonly used in research studies, particularly those examining small degrees of progression or regression of plaque size. However, volumetric calculations are time consuming and of less value for everyday clinical applications of IVUS imaging.

Qualitatively, the echodensity of the plaque on grayscale displays is somewhat related to its tissue content. Using the adjacent adventitia as a visual reference, *echodensity* indicates a plaque is “bright” or “brighter” than

adventitia (closer to the white end of the grayscale), and *echolucency* refers to plaques that appear “darker” than adventitia (closer to the black end of the grayscale). Most plaques are heterogeneous with varying densities, even on the same still frame image (Figure 16.8). Whereas plaques rich in lipid are typically echolucent, echodense ones are typically rich in fibrous tissue and calcification. The association between echodensity and tissue content is not robust because of the overlap between various levels of grayscale and heterogeneous tissue content. As discussed later, advanced analysis of ultrasound backscatter (e.g., virtual histology technology) attempts to overcome the limitations of visual analysis of the reconstructed grayscale images.

Calcified plaques represent a distinct and challenging subset of lesions for interventional cardiologists. IVUS imaging provides significant insights into the presence, extent, and depth of coronary calcification. Typical calcified plaques are very dense and have a back-shadow caused by the complete absorption of the ultrasound

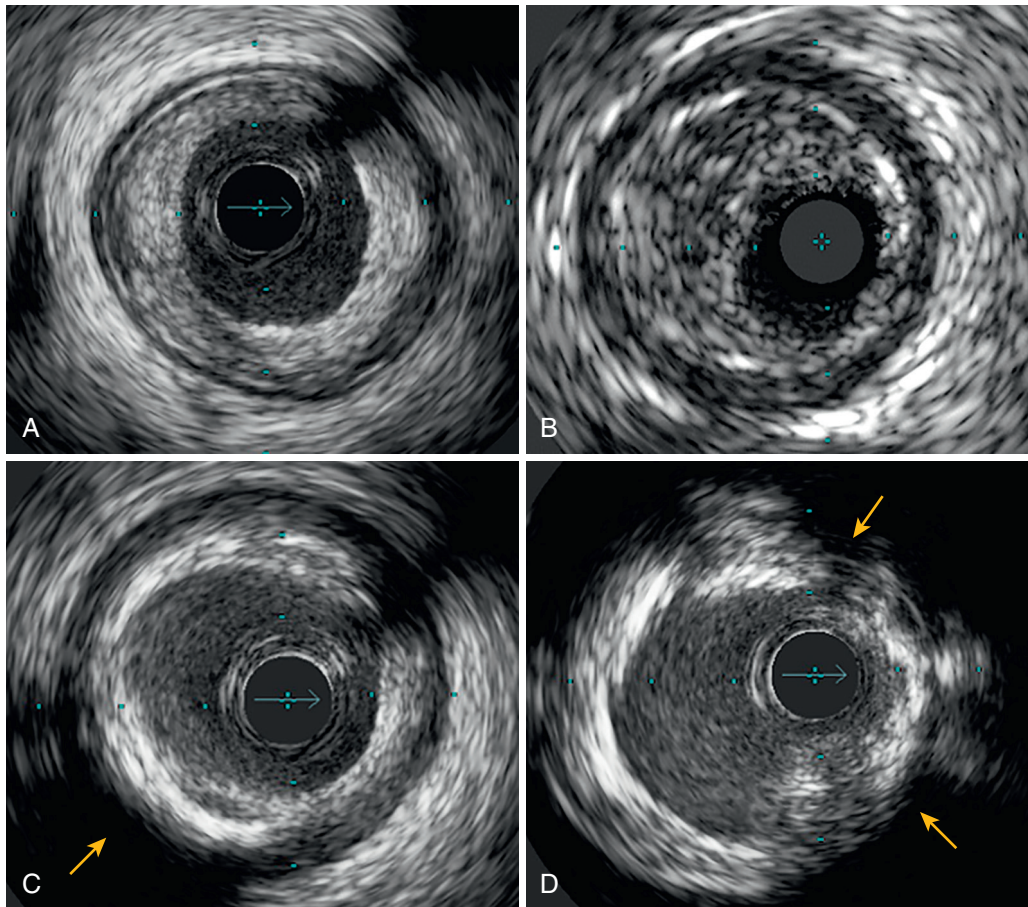


FIGURE 16.8 Typical intravascular ultrasound (IVUS) plaque morphology and distribution. Atherosclerotic plaques are usually classified according to their echodensity on IVUS images. The density of the surrounding adventitia is used as reference. Distribution can also be described according to the thickness of plaque on one wall versus the other. **A**, An example of a concentric echodense plaque with mild to moderate lumen compromise. **B**, An eccentric echolucent plaque with severe luminal narrowing. **C**, The plaque is concentric in distribution but heterogeneous in density. An arc of high echodensity and back shadow (arrow) is indicative of calcification. **D**, More extensive calcification and backshadow involving more than half the circumference of the artery (arrows).

beam.¹³ IVUS imaging is much more sensitive in identifying coronary calcification than fluoroscopy and cine angiography.¹⁴ Calcification is typically quantified by the size of the arc of the artery involved (in degrees) and length of the calcified segment. It is either superficial (directly in contact with speckle of blood flow in lumen) or deep (separated from lumen by a layer of noncalcified plaque), although typically, there are components of both.¹⁵ Calcified nodules are also identified on IVUS images when the calcified plaque is protruding into the lumen with a convex or irregular leading edge.¹⁶

GUIDELINES FOR USE AND APPROPRIATE INDICATIONS

Over the past 2 decades, numerous clinical studies have established a number of acceptable and appropriate applications of IVUS imaging in cardiac catheterization laboratories. The clinical practice guideline for coronary revascularization published by the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions in 2010 and 2021 outline

the recommendations for coronary IVUS imaging, with the recently published document providing updated recommendation based on numerous publications that accumulated over the intervening decade (Table 16.1).^{17,18} European experts provided similar guidance in a consensus document published in 2018.¹¹

The following section reviews the current diagnostic and interventional applications outlined in the guideline statement. In addition, a few more advanced or highly specialized as well as research applications are discussed in detail.

DIAGNOSTIC APPLICATIONS

Ambiguous Angiograms and Intermediate Coronary Lesions

Vessel overlap, vessel tortuosity, eccentric lesions, ostial or bifurcation lesions, and severe calcification constitute the major reasons for suboptimal angiographic visualization of the lumen (see Figures 16.4 and 16.5). In these situations, orthogonal views and operator experience may not be enough to accurately define presence, severity, and

TABLE 16.1 Indications of Coronary Intravascular Ultrasound Imaging Based on American College of Cardiology/American Heart Association/ Society for Cardiovascular Angiography and Interventions Guideline Documents^{17,18}**CLASS I**

- None

CLASS IIa

- Assessment of angiographically indeterminate left main CAD (Level of Evidence: B)
- IVUS imaging and coronary angiography are reasonable 4–6 wk and 1 y after cardiac transplantation to exclude donor CAD, detect rapidly progressive cardiac allograft vasculopathy, and provide prognostic information (Level of Evidence: B).
- In patients with stent failure, IVUS or OCT is reasonable to determine the mechanism of stent failure (Level of Evidence: C).
- In patients undergoing coronary stent implantation, IVUS can be useful for procedural guidance, particularly in cases of left main or complex coronary artery stenting, to reduce ischemic events (Level of Evidence: B).

CLASS IIb

- Assessment of non-left main coronary arteries with angiographically indeterminate coronary stenoses (50%–70% diameter stenosis) (Level of Evidence: B)

CLASS III

- Routine lesion assessment is not recommended when revascularization with PCI or CABG is not being contemplated (Level of Evidence: C).

CABG, Coronary artery bypass grafting; CAD, coronary artery disease; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

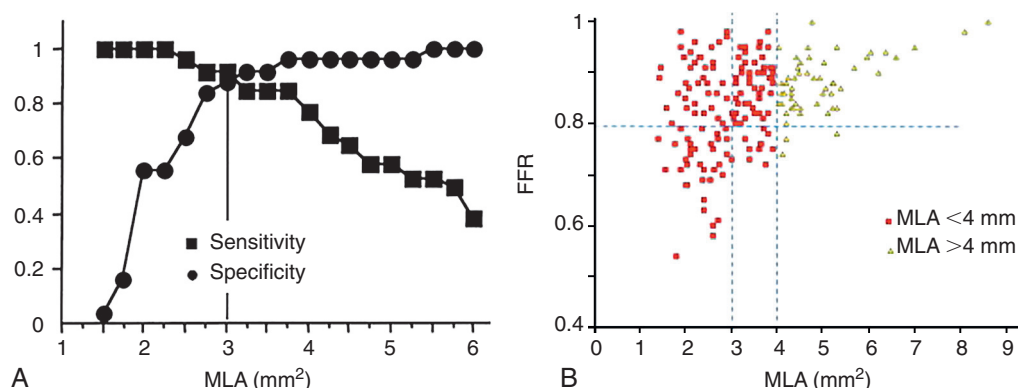


FIGURE 16.9 Role of intravascular ultrasound in defining significance of angiographically intermediate lesions. A threshold of minimal lumen area (MLA) of 3.0 mm² provides the most reasonable compromise between sensitivity and specificity for defining hemodynamically significant lesions, based on fractional flow reserve measurement as the gold standard (A). An MLA exceeding 4.0 mm² has a high negative predictive value as seen in the results of Ben-Dor et al (B). Cross-sectional narrowing and lesion length are other measures that are predictive of hemodynamic significance (not shown). (A, From Takagi A, Tsurumi Y, Ishii Y, et al. Clinical potential of intravascular ultrasound for physiological assessment of coronary stenosis: relationship between quantitative ultrasound tomography and pressure-derived fractional flow reserve. *Circulation*. 1999;100:250-255. B, From Ben-Dor I, Torguson R, Deksissa T, et al. Intravascular ultrasound lumen area parameters for assessment of physiological ischemia by fractional flow reserve in intermediate coronary artery stenosis. *Cardiovasc Revasc Med*. 2012;13(3):177-182.)

distribution of disease. This is particularly important when the lesions are of intermediate (40%–70%) severity in patients with mild or atypical symptoms. In these settings, IVUS imaging provides a tomographic perspective that is independent of the radiographic projection, which allows accurate quantification of lumen size, plaque burden, plaque distribution in relation to branch points, and distribution of calcified plaque.

When an angiographically intermediate lesion (40%–70% diameter stenosis) is encountered, inter- and intraobserver variability are quite high. Further evaluation can be accomplished either by functional assessment (FFR measurement) or by more accurate definition of lumen size using IVUS or OCT imaging. Measurement of FFR accurately defines hemodynamically significant lesions.¹⁹ Multiple prospective randomized trials have validated the use of FFR measurement in clinical decision-making on the need for revascularization versus conservative management.²⁰⁻²²

Intravascular ultrasound measures that are used to define hemodynamically significant lesions have mostly been

benchmarked against established FFR cutoff thresholds. In a small study of 51 lesions, a lesion was considered hemodynamically significant when FFR was less than 0.75. The IVUS measurements that identified such a lesion were minimum lumen area (MLA) less than 3.0 mm² (sensitivity, 83.0%; specificity, 92.3%) and area stenosis greater than 60% (sensitivity, 92.0%; specificity, 88.5%) (Figure 16.9). The combination of both criteria (MLA <3.0 mm² and area stenosis <60%) had 100% sensitivity and specificity.²³ In another study of 53 lesions, a minimal luminal diameter (MLD) of less than 1.8 mm, MLA of 4 mm² or less, and cross-sectional area stenosis of greater than 70% were the best indicators of hemodynamic significance, as determined by an FFR below 0.75.²⁴ Methodologic differences in the measurements of FFR (such as intracoronary vs intravenous administration and use of adenosine vs papaverine for generation of hyperemia) in these two studies may explain the discrepant cutoff values.

As the FFR threshold of less than 0.8 has been adopted more recently to define ischemia-producing lesions and

also to address discrepancies in reference vessel size, a larger retrospective analysis of 205 angiographically intermediate lesions was performed using both IVUS and FFR measurements. FFR was less than 0.8 in 26% of lesions. Overall, there was moderate correlation between FFR and IVUS measurements, including MLA (r , 0.36; P < .001), lesion length (r , -0.43; P < .001), and area stenosis (r , 0.33; P = .01). For the whole sample, an MLA greater than 4.0 mm² had an excellent negative predictive value (>94%), and MLA less than 3.09 mm² was the best determinant of lesions with FFR less than 0.8 (sensitivity, 69.2%; specificity, 79.5%) (see Figure 16.9). The correlation between FFR and IVUS was better for large vessels than small vessels. Depending on reference vessel diameter, threshold MLA values for ischemia-producing lesions (FFR < 0.8) were MLA less than 2.4 mm² in small vessels, MLA less than 2.7 mm² in medium sized vessels, and MLA less than 3.6 mm² in large vessels (Figure 16.10).²⁵

In other situations, the resolution of cine angiography may not be adequate to identify clinically important findings. Examples include plaque erosion with a small overlying thrombus or a spontaneous dissection with an intimal tear or intramural hematoma (Figure 16.11 and Video 16.1). In both these examples, the term *MINOCA* (myocardial infarction with no obstructed coronary arteries) is used to describe what, on the surface, appears as an angiogram without significant narrowing coupled with a clinically distinct and significant event such as a non-ST-segment elevation myocardial infarction (NSTEMI). These scenarios demonstrate the significant role of intravascular imaging in enhancing our understanding of coronary event pathophysiology.

Evaluation of Left Main Coronary Artery Indeterminate Lesions

The angiographic severity of left main coronary artery (LMCA) lesions is almost always difficult to quantify.²⁶ Visualizing the ostium and most proximal part of the vessel depend on the “reflux” of contrast into the aortic cusp. “Streaming” of contrast from the injection vortex can give a false impression of luminal narrowing near the tip of the injecting catheter. When the whole length of the LMCA is diseased, the absence of a near-normal reference segment complicates the visual or automated quantification of stenosis severity. Furthermore, disease in the bifurcation or trifurcation into daughter branches is often complex in topography and is frequently concealed by the overlap of the branches or contrast filling the aortic cusp in different projections (Figure 16.12). Thus, reproducibility of quantitative angiography of the LMCA is worse than that of all other coronary arterial segments.²⁷ For these reasons, IVUS imaging is commonly used for better delineation of LMCA stenoses.

Similar to non-LMCA lesions, a few studies were based on correlating cutoff values of IVUS measurements with FFR measures of hemodynamic significance of LMCA stenosis. In a study of 55 patients with angiographically ambiguous LMCA, both FFR and IVUS measurements were performed. The 2 IVUS measurements that correlated best with hemodynamically significant lesions as determined by FFR were MLD less than 2.8 mm (sensitivity and specificity of 93% and 98%, respectively) and MLA less than 5.9 mm² (sensitivity, 93%; specificity, 95%) (Figure 16.13).²⁸

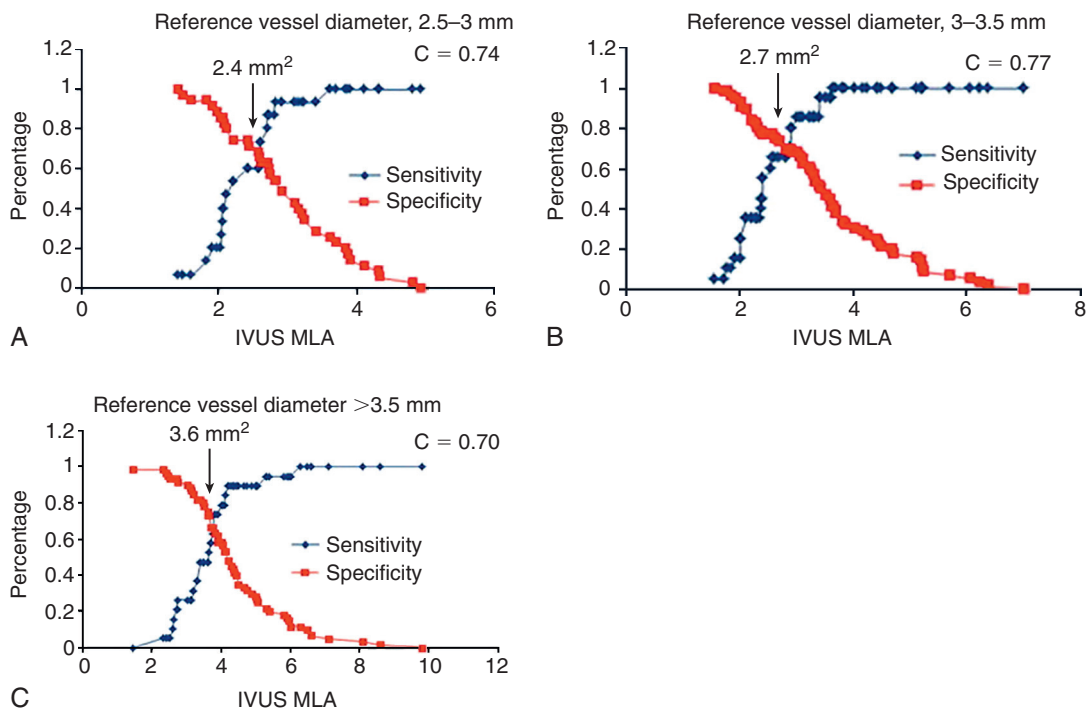


FIGURE 16.10 A–C, Role of intravascular ultrasound imaging (IVUS) in defining significance of angiographically intermediate lesions. The minimal lumen area (MLA) threshold used to correlate with hemodynamic significance as assessed by fractional flow reserve varies according to the reference vessel size. The threshold for hemodynamically significant stenosis is 2.4 mm² in small vessels (panel A), 2.7 mm² in medium sized vessels (panel B) and 3.6 mm² in large vessels (panel C). (From Ben-Dor I, Torguson R, Deksis T, et al. Intravascular ultrasound lumen area parameters for assessment of physiological ischemia by fractional flow reserve in intermediate coronary artery stenosis. *Cardiovasc Revasc Med*. 2012;13(3):177-182.)

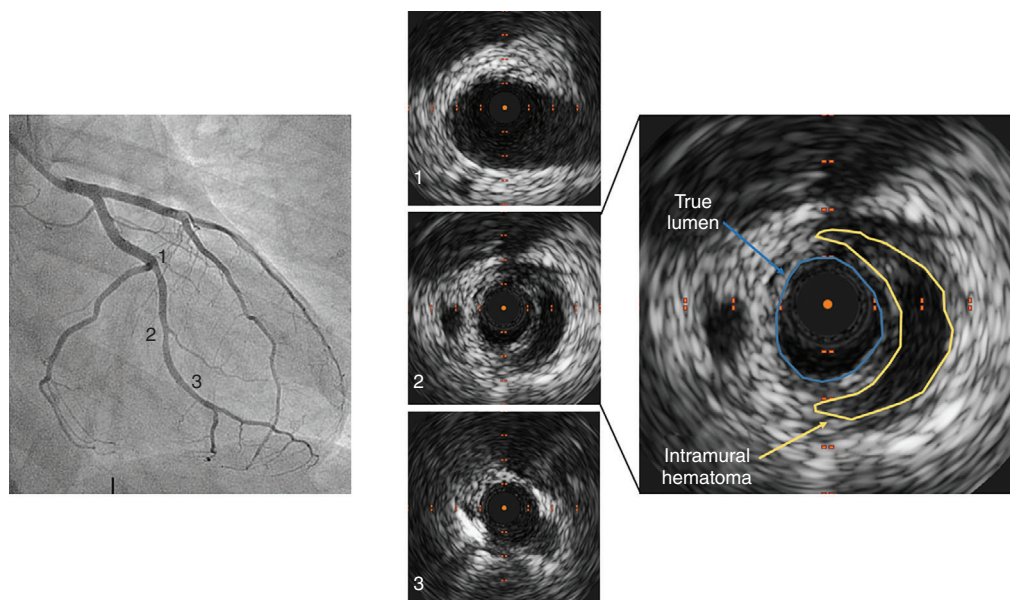


FIGURE 16.11 Role of intravascular ultrasound (IVUS) imaging in identifying underlying pathology not discernable angiographically. *Left*, a right anterior oblique caudal angiogram obtained after a non-ST-segment elevation myocardial infarction event in a 38-year-old woman with hypertension. No significant obstructive lesions are noted. There is a mild irregularity and possibly some angiographic haziness in the OM branch of the circumflex artery (marked 2 on the angiogram). Reference and branching points proximal and distal to that area are marked 1 and 3, respectively. IVUS imaging of the suspicious segment shows the IVUS catheter artifact in the center of the true lumen with a surrounding and crescent-shaped echolucent space, representing an intramural hematoma (*central image*, zoomed in and annotated on the *right*). Images from reference segments 1 and 3 demonstrate branching points confirming the presence of the IVUS catheter in the true lumen.

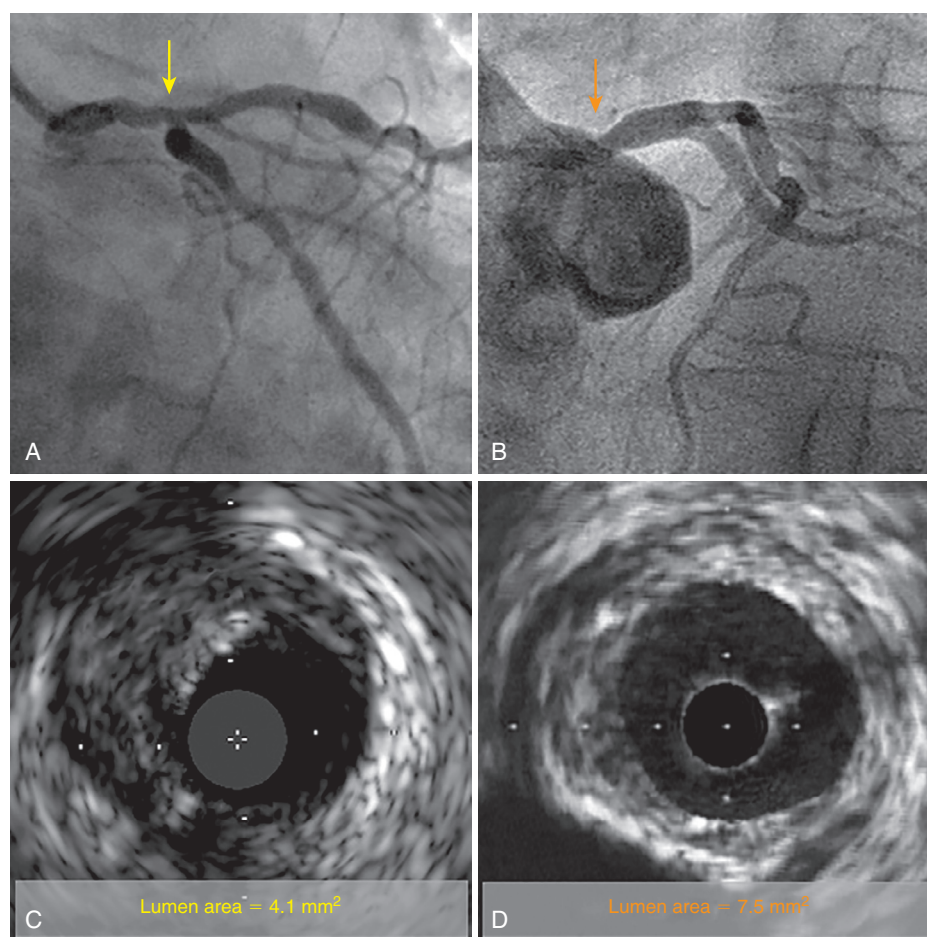


FIGURE 16.12 Examples of intravascular ultrasound (IVUS) imaging of left main disease. **A**, The caudal angiographic projection reveals a mild distal left main narrowing (*arrow*) in a patient with an early positive stress test. **C**, IVUS imaging reveals a significant eccentric plaque with a minimum lumen area (MLA) below the threshold of hemodynamic significance typically used ($<5.9\text{mm}^2$). These findings prompted referral to coronary bypass surgery. **B**, An ostial left main lesion is seen on the angiogram without evidence of pressure dampening and in a patient with a marginally positive stress test. **D**, IVUS imaging reveals an eccentric calcified plaque but a large uncompromised lumen. These findings led to deferral of any revascularization.

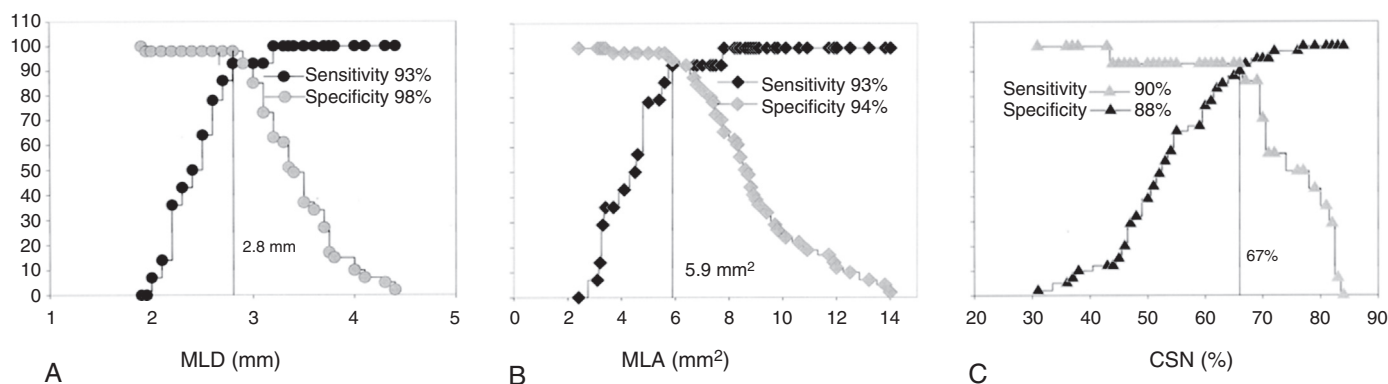


FIGURE 16.13 Defining significance of left main disease based on intravascular ultrasound (IVUS) imaging. Sensitivity and specificity curves of ischemic threshold of fractional flow reserve (FFR) and IVUS parameters in cases of ambiguous left main coronary disease. The FFR cut point was 0.75. Best agreement was found when minimum lumen diameter was 2.8 mm or less (A), minimum lumen area (MLA) was 5.9 or less mm² (B), or cross-sectional narrowing (CSN) was 67% or less (C). MLD, Minimum lumen diameter. (From Jasti V, Ivan E, Yalamanchili V, et al. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation*. 2004;110:2831-2836.)

In another series of 122 patients with intermediate LMCA stenosis, patients were followed for 1 year after a clinical decision to defer revascularization. Similar to the FFR based studies, the MLD was the most important predictor of adverse cardiac events. A threshold MLD of 3 mm appeared to provide the best cutoff between those who developed clinical events and those who did not.²⁹ Other patient series demonstrated the safety of deferring revascularization in patients with LMCA stenosis when the minimum lumen area was greater than 7.5 mm².³⁰

Evaluation of Transplant Vasculopathy

Cardiac allograft vasculopathy (CAV) is a disease of unclear etiology that affects the coronary arteries of the transplanted heart and is characterized (at least in part) by progressive intimal proliferation of coronary arteries.³¹ Because of its diffuse nature, the sensitivity of coronary angiography for detection of CAV is appreciably lower than its sensitivity in detection of the more segmental atherosclerotic lesions.^{32,33} IVUS imaging provides a useful and safe tool to study the early development and progression of CAV.³⁴⁻³⁶ CAV is commonly defined as a site where the intimal thickness is 0.5 mm or greater,^{37,38} although a cutoff value of 0.3 mm is also used as a cutoff to diagnose earlier lesions.³⁹

Intravascular ultrasound imaging of coronary arteries soon after transplantation has demonstrated that arteries that appear angiographically normal may contain evidence of early donor atherosclerosis. In one series with a mean donor age of 32 years, atherosclerotic lesions (maximal intimal thickness ≥ 0.5 mm) were detectable in more than 50% of patients. Donor atherosclerotic lesions are focal and noncircumferential, may be calcified, and most commonly involve the proximal segments.⁴⁰ The presence of donor atherosclerosis does not seem to predispose to development of CAV.^{41,42}

On serial IVUS studies with matched segments, CAV progression initially manifests as increasing intimal thickening associated with compensatory positive remodeling. Lumen compromise over a 5-year follow-up period can also be the result of a negative remodeling response.⁴³ Several studies have demonstrated an association between disease

severity as assessed by IVUS and the clinical outcome in transplant recipients.^{44,45} Serial studies allow the evaluation of disease progression, which is another important predictor of outcome. In a serial study of 143 patients followed for an average of 5.9 years, IVUS evidence of rapid progression of CAV (defined as a ≥ 0.5 -mm increase in intimal thickness in the first year after transplantation) was a powerful predictor of all-cause mortality and MI. Patients with rapidly progressive CAV had a higher mortality rate than those without (26% vs 11%; $P = .03$). Death and nonfatal MI were also more frequent among those with rapid progression (51% vs 16%; $P < .0001$).⁴⁶

Intravascular ultrasound imaging has also been used in evaluation of therapies directed toward control of CAV. The beneficial effects of pravastatin and everolimus in delaying the progression have been shown using IVUS imaging.^{47,48}

INTERVENTIONAL APPLICATIONS

In addition to the contribution of intracoronary IVUS imaging to better understanding of pathoanatomical complexities of coronary artery disease, it has also been instrumental in more accurate and sophisticated understanding of the impact and mechanism of action of interventional devices. Since the mid-1990s, interventional operators began to guide the interventional procedure and its endpoints using IVUS imaging. This wealth of information resulted in improvement in device design and refinement of procedure techniques. Subsequently, the knowledge gained by operators from IVUS imaging became assimilated in the technical approaches. Widespread and routine use of IVUS imaging during interventional procedures tapered down to a more selective approach in Europe and North America, less so in East Asia, where intracoronary imaging remained a standard component of interventions. Contemporary evidence demonstrates clear improvement in hard endpoints such as major adverse cardiovascular event (MACE), target-vessel revascularization (TVR), and target lesion revascularization (TLR) have reignited the discussion about the need for more widespread and routine use of IVUS or OCT in guiding interventional procedures and optimizing results.

Selection of Intermediate Lesions for Intervention

Recent data confirmed the validity of using IVUS measurements in identification and guiding treatment of hemodynamically significant lesions with intermediate angiographic stenosis severity. FLAVOUR (Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy for Clinical Outcomes in Patients with Intermediate Stenosis) is a large prospective randomized trial that enrolled 1682 patients with stable coronary disease and angiographically intermediate lesions (diameter stenosis 40-70%). Investigators sought to demonstrate the non-inferiority of identifying and treating these intermediate lesions based on IVUS imaging compared to the traditional gold standard: FFR measurement. Patients randomized 1:1; FFR ($n = 838$) vs. IVUS ($n = 844$). In the FFR group, PCI was indicated if $FFR \leq 0.8$ and considered optimized if post-PCI $FFR \geq 0.88$. In the IVUS group, PCI was indicated if minimal luminal area (MLA) $\leq 3 \text{ mm}^2$, or >3 to 4 mm^2 with plaque burden $>70\%$ and considered optimized if post-PCI MLA $\geq 5.5 \text{ mm}^2$ and plaque burden at stent edge $\leq 55\%$. The primary endpoint of the study was all-cause death, myocardial infarction, or revascularization at 24 months. The results confirmed non-inferiority of the IVUS criteria, with event rates almost identical between the IVUS and FFR groups (8.5% and 8.1%, $p=0.015$ for non-inferiority). There was no significant difference in any of the components of the composite endpoint, nor in the quality of life objective assessments. Interestingly, optimal PCI outcomes could only be achieved in about half the patients, in both groups.^{48b}

Vessel Sizing and Lesion Preparation

Use of properly sized devices (e.g., balloons, stents, atherectomy burrs) is essential to achieve optimal procedural outcomes. Underestimation of reference vessel size and use of undersized devices lead to suboptimal outcomes such as early recoil, inadequate procedural lumen gain, or stent complications such as stent underexpansion or strut malapposition. On the other hand, an oversized device increases the risk of dissection or rupture.

As previously discussed, IVUS imaging frequently reveals significant disease burden in vessels that appear angiographically normal or mildly diseased, thus the true size of the reference vessel can be underestimated (see [Figures 16.1](#) and [16.7](#)). Certain clinical scenarios are associated with significant underestimation of angiographic reference vessel size. Examples include percutaneous coronary intervention (PCI) in the setting of acute myocardial infarction (MI) (higher degree of coronary vasomotor tone) and chronic total occlusion (CTO; distal segments are underfilled and diffusely diseased). In these situations, adequate coronary vasodilators and IVUS imaging can accurately delineate the reference vessel size, which is the most important determinant of device size selection. Often, after IVUS imaging and quick quantitative analysis, a larger balloon or stent size is accurately and safely selected for use.

It is important to use IVUS imaging for vessel sizing judiciously. The reference vessel size is determined by the lumen diameter in the reference segments (i.e., segments that have no or minimal disease in the vicinity of the lesion to be treated). Using the EEM dimension at the reference or at the

site of the lesion will result in overestimation of the vessel size because EEM diameters reflect a degree of positive remodeling in most cases. This can result in device oversizing and should be avoided or used with caution. The operator should focus on lumen size, with some adjustment depending on plaque burden. A recent practice to simplify the postdilation balloon size selection suggests using lumen diameter for stent size with rounding up by 0.25 mm or using EEM diameter with rounding down 0.25 mm.⁴⁹

As discussed later, the plaque burden at the edges of the stent have been gaining more attention as an important predictor of outcome. During pre-PCI IVUS interrogation, identifying distal and proximal landing zones where plaque burden is minimal will typically alter the length of selected stent as assessed by angiography alone. Stent reference segments with no or minimal disease will reduce the risk of edge dissections and are associated with reduced risk of restenosis.⁵⁰

Plaque composition, particularly calcification, can also have a significant impact on procedural planning. Heavy calcification can preclude stent delivery or lead to stent underexpansion, which increases the risk of stent thrombosis and restenosis. Understanding the detailed extent of calcification is important to decide whether plaque modification is needed before stenting. Modification of heavily calcified plaques can be achieved using rotational atherectomy, intravascular lithotripsy, or even cutting balloons. Recently, efforts to define the need for plaque modification identified four factors that can be used in a scoring system: if the arc of superficial calcium is 360 degrees (circumferential), if it is 270 degrees but involving a longer than 5-mm-long segment, in the presence of a calcified nodule, and in particular when the vessel diameter is less than 3.5mm. The higher scores predicted a higher likelihood of suboptimal stent expansion and hence would suggest that plaque modification in these settings is desirable⁵¹ ([Figure 16.14](#)).

Intravascular Ultrasound Imaging in Coronary Stenting

Historically, IVUS imaging has been instrumental in optimizing the technique of coronary stenting as it is currently practiced. Initial IVUS observations in the early 1990s revealed that the technique of stents were frequently inadequately expanded and not fully opposed to the arterial wall despite satisfactory angiographic results.^{52,53} These observations led to major refinements in the technique of stenting, most notably higher pressure postdilations and the use of upsized balloons. Coupled with the introduction of dual antiplatelet therapy, these technical improvements resulted in a significant reduction in the incidence of stent thrombosis.⁵⁴

A few terms commonly used in the discussion of IVUS imaging and stenting need to be defined. *Stent expansion* refers to the size of the stent lumen achieved after the stent is deployed and postdilated. That can be expressed in terms of MLD or more frequently MLA. Expansion is also indexed to the size of the reference segments, in which MLD or MLA are divided by the mean diameter or area of the reference vessel to express a percentage of

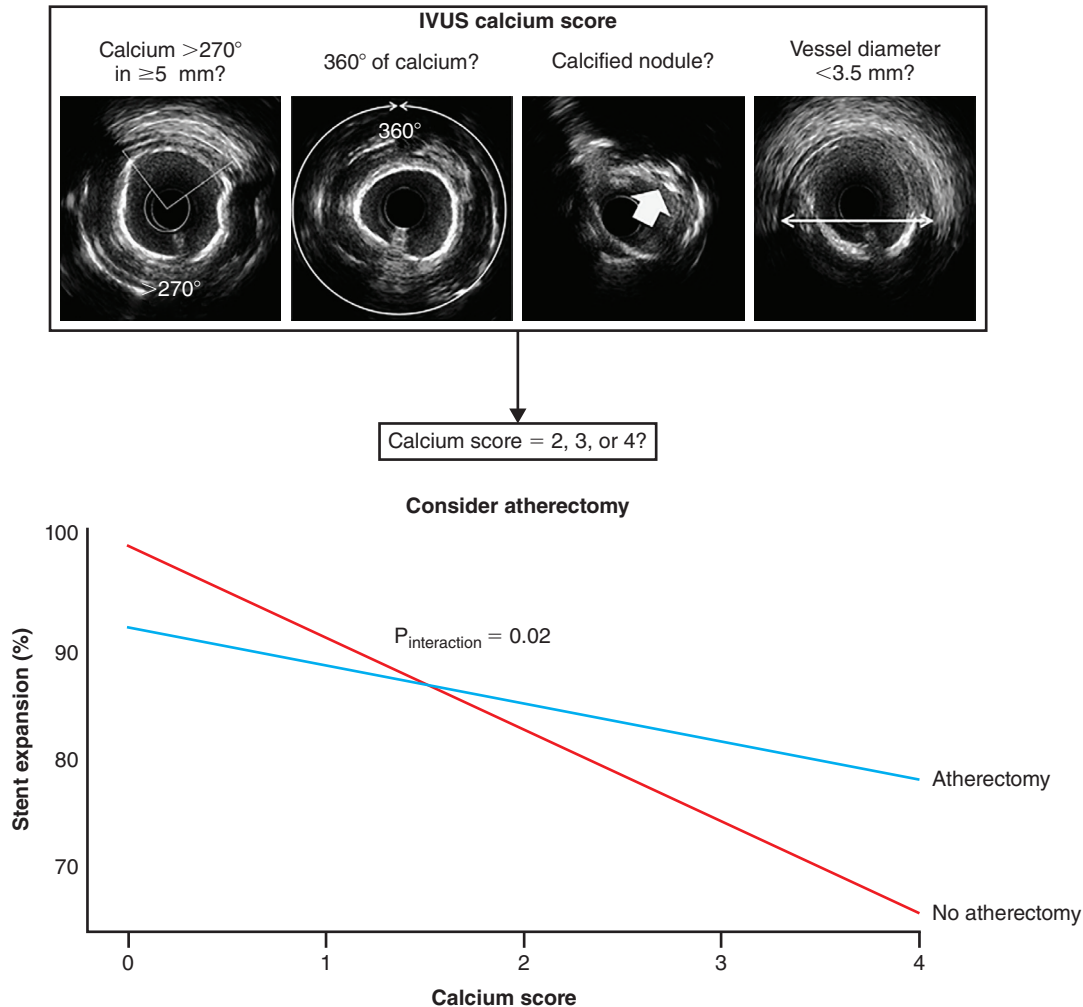


FIGURE 16.14 Development of an intravascular ultrasound (IVUS) calcium score and its impact on stent expansion. *Top panels* are examples of the various IVUS findings incorporated into the development of a scoring system defining the severity of calcification and the potential need for pre-stenting plaque modification. The *lower panel* demonstrates the worsening stent expansion with higher scores. Atherectomy before stenting may blunt this effect to some extent, with the two curves intersecting between scores of 1 and 2. (From Zhang M, Matsumura M, Usui E, et al. Intravascular ultrasound-derived calcium score to predict stent expansion in severely calcified lesions. *Circ Cardiovasc Interv.* 2021;14(10):e010296.)

the reference. Stent MLA is an important predictor of restenosis as will be discussed later. *Stent or strut apposition* describes the contact between the stent struts and the underlying arterial wall. This is a qualitative metric of stenting that is detected with advanced imaging such as IVUS or OCT. It is related but not synonymous with stent expansion. It is common to see a well-opposed but under-expanded stent (e.g., when the stent is slightly under-sized or if a rigid lesion is not adequately predilated; [Figure 16.15](#)). *IVUS-guided stenting* refers to the strategy of using IVUS imaging to optimize all aspects of the stenting procedure (i.e., using IVUS to assess vessel size, facilitate lesion preparation, assess adequate expansion and apposition, confirm result after postdilation, and ensure absence of complications in the reference segments; [Figure 16.16](#)).

Specific criteria to define optimal stent expansion were developed out of multiple observations studies that correlated final IVUS measurements with angiographic or clinical outcome.⁵⁵⁻⁵⁹ The general consensus among those studies is that minimum in-stent lumen dimensions are the most important predictors of restenosis.⁶⁰

Bare-Metal Stents

In bare-metal stents (BMSs), a minimum stent area smaller than 6 mm^2 was associated with the highest rates of restenosis and need for repeat revascularization.^{55,59} The lumen area within the stented segment is primarily determined by the target vessel size, explaining the relatively higher rates of restenosis in smaller vessels despite the achievement of excellent procedural results in the majority of cases ([Figure 16.17](#)).

The strategy of IVUS-guided bare-metal stenting has been evaluated in several nonrandomized registries⁶¹⁻⁶⁵ and some randomized trials.⁶⁶⁻⁶⁸ There is general consensus that this did not alter the incidence of death and nonfatal MI, but it did consistently lead to a larger in-stent lumen dimensions as a result of higher pressure, balloon upsizing, or both. Whether this led to a reduction in clinical restenosis and need for repeat revascularization remains controversial. Results have not been consistent, and favorable results were observed more in the registries than in the randomized trials.

Drug-Eluting Stents

Early in the DES era, several IVUS studies and substudies were performed to better understand the predictors and

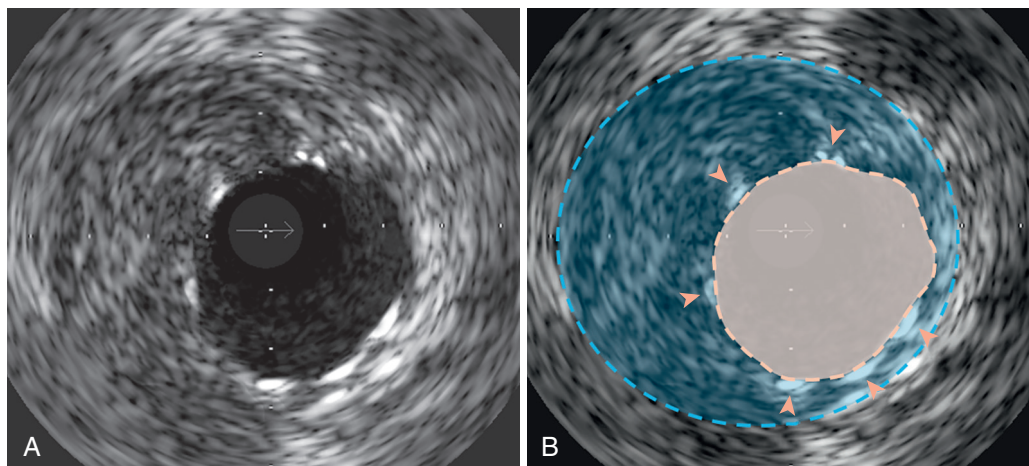


FIGURE 16.15 Stent expansion and strut malapposition. An intravascular ultrasound image acquired after an undersized stent is deployed in the mid right coronary artery. The same image is shown in **A** and **B**, with the electronic tracings of the stent lumen and the external elastic membrane (EEM) superimposed on **B**. The dense metallic struts of the stent are seen in **A**. The small size of the stent lumen (*orange*) within the large EEM area (*blue*) represents stent underexpansion and is probably caused by underestimation of vessel size. However, the stent struts (*arrowheads*) are all well opposed to the border of the plaque, and thus there is no evidence of malapposition.

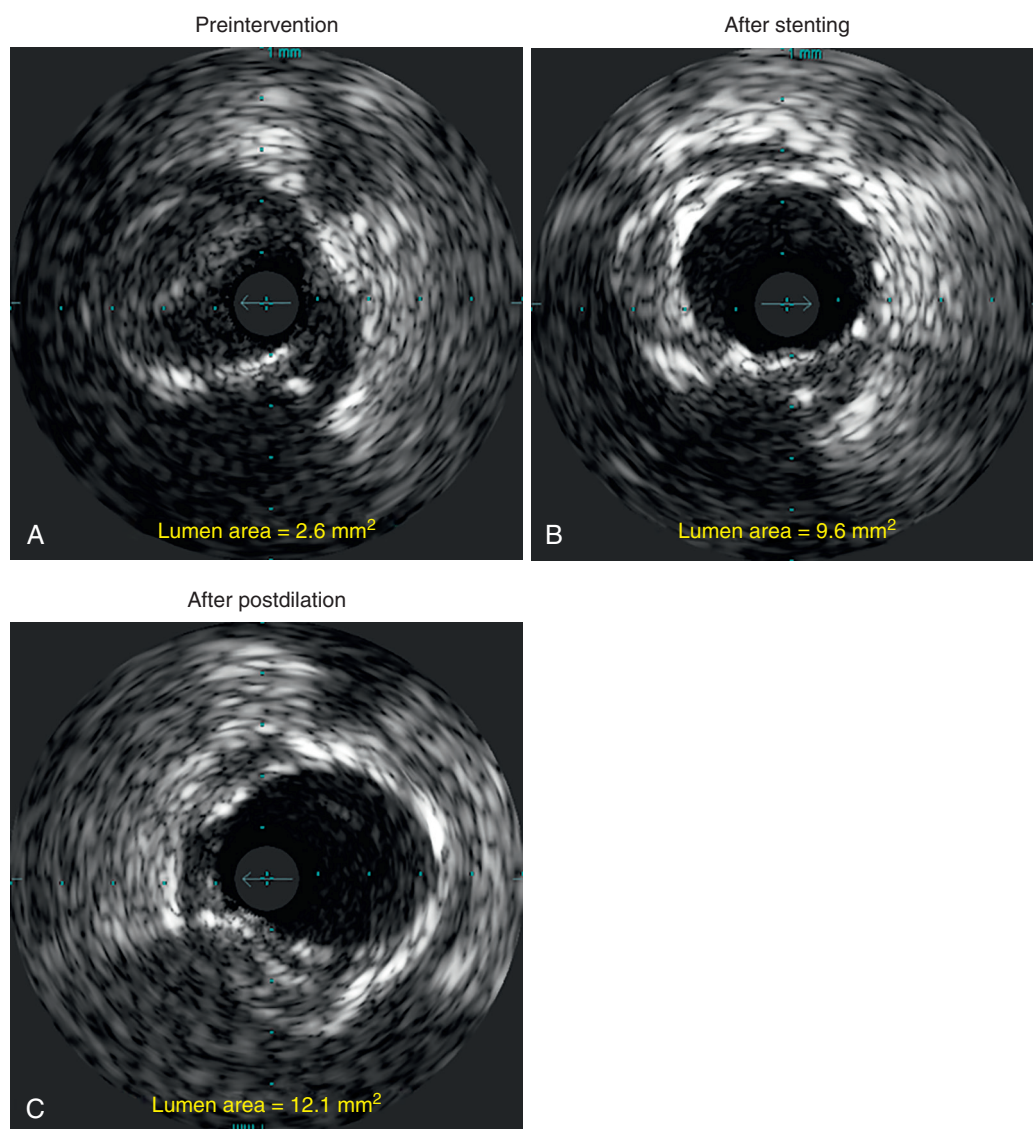


FIGURE 16.16 Example of intravascular ultrasound (IVUS)-guided stenting. Preintervention IVUS (**A**) reveals large plaque burden with mostly echolucent content but with eccentric calcification. After balloon predilation and stent deployment at moderately high pressure (**B**), the struts are well opposed, but the stent lumen area appears small compared with the size of the vessel. Further postdilation using an appropriately sized noncompliant balloon improves minimum stent lumen area (**C**, image rotated to facilitate comparison).

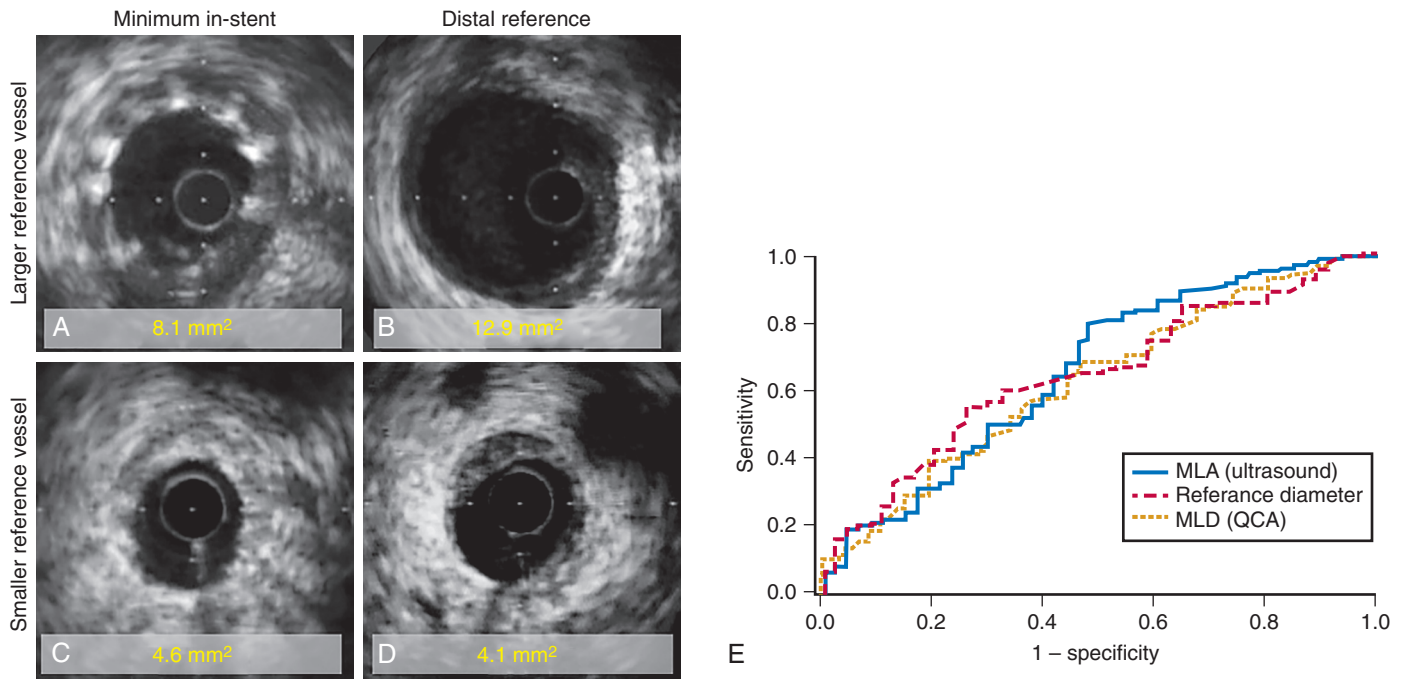


FIGURE 16.17 Impact of reference vessel size on outcome of stenting. The final stent lumen size is primarily determined by the reference vessel size. In larger vessels (intravascular ultrasound [IVUS] images, **A** and **C**), a larger stent minimum lumen area (MLA) can be obtained even if there is a residual stenosis compared with the reference vessel. On the contrary, the stent lumen will be small even if there is no residual stenosis in a smaller reference vessel (bottom IVUS images, **B** and **D**). Receiver operator curves (**E**) demonstrate that the minimum stent lumen area is not a better predictor of target vessel revascularization than the reference vessel diameter, emphasizing the importance of vessel size in determining outcome. MLD, Minimum lumen diameter; QCA, quantitative coronary angiography. (From Ziada KM, Kapadia SR, Belli G, et al. Prognostic value of absolute versus relative measures of the procedural result after successful coronary stenting: importance of vessel size in predicting long-term freedom from target vessel revascularization. *Am Heart J*. 2001;141:823-831.)

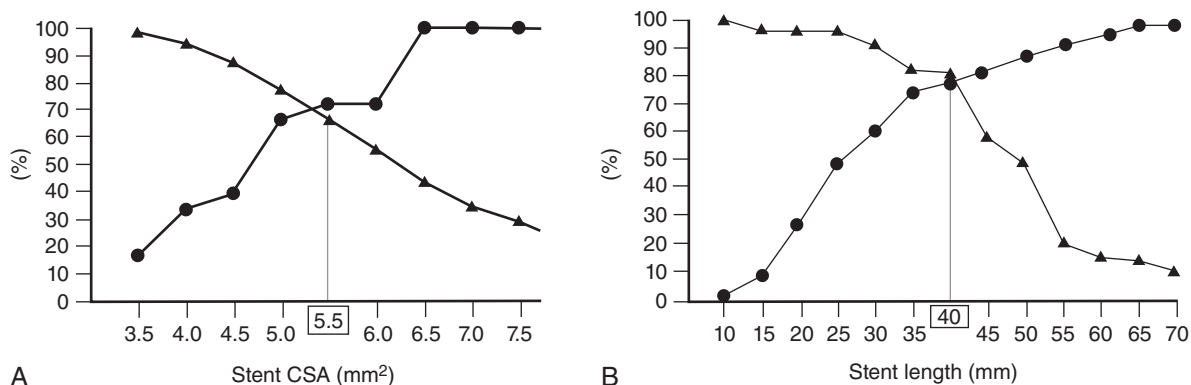


FIGURE 16.18 Impact of minimum cross-sectional stent area (**A**) and stent length (**B**) on angiographic restenosis in the drug-eluting stent era. Data from the follow-up of sirolimus-eluting stents demonstrate the sensitivity and specificity of minimum stent area and stent length on rate of angiographic restenosis. Restenosis increases with smaller stent area and increasing stent length. An intravascular ultrasound minimum cross-sectional stent area (CSA) of 5.5 mm² and stent length of 40 mm seem to provide the best cutoff value with acceptable sensitivity and specificity for predicting restenosis. Triangles, sensitivity; circles, specificity. (From Hong MK, Mintz GS, Lee CW, et al. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. *Eur Heart J*. 2006;27:1305-1310.)

mechanisms of DES restenosis. In addition, there was significant interest in understanding mechanisms of stent thrombosis and the insights that IVUS imaging can provide in these settings.

Intravascular ultrasound imaging studies of the first generation sirolimus-eluting stents (SESts) demonstrated that a postprocedural minimum stent area of less than 5 to 5.5 mm², as well as a stent length smaller than 40 mm, were the most important predictors of angiographic binary restenosis at 6 to 9 months (Figure 16.18).^{69,70} A larger analysis of a number of IVUS substudies performed within the TAXUS trial program examined the outcomes of the paclitaxel-eluting stents (PESs).⁷¹ This included 1580

PESs and control group patients. After the procedure, the stent MLA was similar in PESs and BMSs (6.6 ± 2.5 mm² vs 6.7 ± 2.3 mm²; *P* = .92). At 9-months, in-stent restenosis was significantly lower in the PES group (10% vs 31%; *P* < .0001). Postintervention stent MLA by IVUS was the independent predictor of subsequent restenosis in both the PES and control BMS groups (*P* = .0002 for PESs and *P* = .0002 for BMSs). The optimal thresholds of postprocedure IVUS MLA that best predicted stent patency at 9 months were 5.7 mm² for PESs and 6.4 mm² for BMSs.

A specific high risk group of patients in whom IVUS guidance has a valuable role are those undergoing unprotected LMCA stenting. In the MAIN-COMPARE (Revascularization



for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry, data from approximately 1000 stable patients undergoing unprotected left main stenting were compiled. IVUS guidance was used in 80% of cases. The 3-year outcomes were compared between the two groups using propensity-score matching in the entire population and separately in those receiving DESs. In 201 matched pairs of the overall population, there was a trend toward reduced mortality rate with IVUS guidance compared with angiography guidance, but this did not reach statistical significance (6.0% vs 13.6%; Cox-model $P = .061$). In the 145 matched pairs of patients receiving DESs, the mortality rate was lower with IVUS guidance (4.7% vs 16.0%; log-rank $P = .048$; hazard ratio [HR], 0.39; 95% confidence interval [CI], 0.15–1.02; Cox model $P = .055$). Although the statistical significance of the benefit appears marginal and the underlying mechanism is unclear, it may be hypothesized that optimal expansion and apposition achieved by IVUS guidance may reduce the risk of late and very late stent thrombosis with DES.⁷² Data from the Swedish registry demonstrated similar outcomes, emphasizing the role of IVUS guidance in left main stenting.⁷³

Although nonrandomized, the ADAPT-DES (Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents) trial provided good evidence of more significant advantages to IVUS guidance of DES procedures, demonstrating reduced risk of stent thrombosis, MI, and major adverse events. This was a prospective, multicenter registry of 8583 patients receiving DES, of whom 3349 (39%) were enrolled in a pre-specified IVUS substudy. The study aimed to determine the frequency, timing, and correlates of early and late stent thrombosis. Patients in the IVUS imaging arm were more likely to have acute coronary syndrome (ACS). IVUS guidance led to a modification of the intended procedure in 74% of cases (larger stent, longer stent, additional stent, additional postdilation, or higher pressures). After 1 year of follow-up, definite or probable stent thrombosis occurred in 18 (0.6%) patients in the IVUS group versus 53 (1.0%) in the non-IVUS group (HR, 0.4; 95% CI, 0.20–0.7; $P = .003$). Other adverse clinical outcomes were significantly reduced in the IVUS guided arm (Table 16.2). After propensity matching, use of IVUS remained an independent predictor of freedom from probable or definite stent thrombosis.⁷⁴

Strut Malapposition

Because of the heightened awareness and concern about DES thrombosis events, the clinical impact of strut malapposition may be significant, and a lower threshold for IVUS examination may be justifiable after stenting

(Figure 16.19 and Video 16.2). IVUS studies have demonstrated evidence of incomplete apposition of DES struts, more commonly seen at the distal stent edge than at the proximal or mid segments. Possible explanations include mismatch between size of the lumen at the reference segment and the selected stent size. Lesion calcification is also another predictor of malapposition observed on IVUS studies.^{75,76}

It is unclear whether minor strut malapposition is related to acute or subacute DES thrombosis, although evidence for this appear circumstantial. In a small retrospective study of patients who returned with late DES thrombosis, the prevalence of strut malapposition was 77% compared with 12% in a control group of DES patients whose stents were imaged at 8 months during routine follow-up and who did not have documented stent thrombosis. The highly statistically significant difference suggests that strut malapposition may have a role in precipitating this catastrophic complication.⁷⁷ However, other studies show that early strut malapposition may not be related to early thrombosis. In a small retrospective IVUS study, 15 patients with thrombosis and 45 control patients were examined. There was no difference in the prevalence of malapposition. However, stent MLA was significantly smaller in those who developed stent thrombosis ($4.3 \pm 1.6 \text{ mm}^2$ vs $6.2 \pm 1.9 \text{ mm}^2$; $P < .001$) compared with the matched control patients. Additionally, severe reference segment disease was more common in the stent thrombosis group (67% vs 9%; $P < .001$).⁷⁸ This highlights the importance of reference segment disease, which operators should consider carefully after stenting. Frequently, an additional stent to treat a severely diseased reference segment may avoid this concern.

Strut malapposition is not always a residual finding detected immediately after stent implantation. The phenomenon of late malapposition has also been described on follow-up IVUS imaging. That phenomenon has been estimated to occur in approximately 5% of BMS procedures but did not appear to have any clinical consequences.⁷⁹ Late malapposition has increased in prevalence with the use of DESs. In a recent analysis of 705 lesions in 557 patients, the incidence was 12% in the overall population, with a higher prevalence in patients with longer stents, those who received DES in context of acute MI, or after CTO.⁸⁰ In this series, there was no evidence of increased clinical events for a period of 10 months after the identification of late strut malapposition. These findings suggest that strut malapposition is of particular concern in situations in which there is difficulty in selecting an appropriate stent size, such as in long and diffusely diseased segments, stenting in the setting of acute MI, CTOs, or in case of a

TABLE 16.2 ADAPT-DES Major Cardiac Adverse Outcomes within 1 Year of Follow-Up

	IVUS GROUP (%)	NON-IVUS GROUP (%) (n = 3343)	HR (95% CI) (n = 5234)	P VALUE
Probable or definite stent thrombosis	0.6	1.0	0.4 (0.2–0.7)	0.02
MI	2.5	3.7	0.7 (0.5–0.9)	0.002
Ischemic TVR	2.4	4.0	0.6 (0.2–0.8)	0.0001
MACE (death, MI, stent thrombosis)	3.1	4.7	0.7 (0.6–0.9)	0.0006

ADAPT-DES, Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents; CI, confidence interval; HR, hazard ratio; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular event; MI, myocardial infarction; TVR, target vessel revascularization.

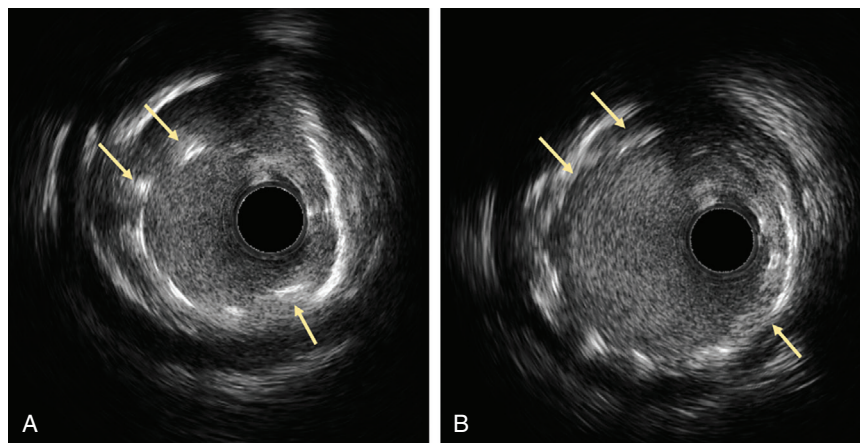


FIGURE 16.19 Strut malapposition. **A**, Intravascular ultrasound imaging after stenting reveals significant strut malapposition (arrows), probably caused by underestimation of vessel size during stent selection. **B**, Subsequent postdilation using a larger noncompliant balloon results in complete apposition, with obliteration of the space between the stent struts and the vessel wall (arrows) and larger stent lumen.

large vessel size mismatch between proximal and distal reference segments. Although it is not definitive that this phenomenon is related to DES late thrombosis, it is prudent to optimize stent expansion and apposition with IVUS guidance in these situations.

Optimal Intravascular Ultrasound-Guided Stenting and Clinical Outcomes

Numerous observational and randomized trials have demonstrated improved outcomes of IVUS- versus angiography-guided stenting over the past decade. The improvement in outcomes has been primarily driven by a reduction in TVR or TLR. Given that IVUS-guided stenting has consistently yielded larger minimum stent area, these conclusions were not surprising. Interestingly, other adverse events have been shown to be reduced by IVUS guidance as well, including cardiac mortality. Although the reduction in mortality rate has been more likely to find in observational datasets, with the possibility of selection bias, there has been some suggestion of the same finding in post-hoc analyses of randomized datasets as well.

Several major studies have established the advantages of IVUS-guided stenting in improving outcomes. The IVUS-XPL (Impact of Intravascular Ultrasound Guidance on the Outcomes of Xience Prime Stents in Long Lesions) study was prospective, randomized, and multicenter. It included 1400 Korean patients undergoing stenting for long lesions

(requiring ≥ 28 -mm stents). At 1 year, MACEs occurred in 19 patients (2.9%) undergoing IVUS-guided and in 39 patients (5.8%) undergoing angiography-guided stenting (HR, 0.48; 95% CI, 0.28–0.83; $P = .007$). Most of the difference was driven by target lesion revascularization, with no significant difference in cardiac death or target lesion-related MI.⁸¹

The ULTIMATE study (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in All-Coroner Coronary Lesions) is one of the most contemporary and large “all comer” IVUS- versus angiography-guided stenting randomized clinical trials in the field. It included more than 1400 all-comer patients randomized to IVUS- versus angiography-guided stenting. The primary endpoint was target vessel failure (TVF) at 12 months, including cardiac death, target-vessel MI, and clinically driven TVR. Criteria for optimal stenting were predefined, and procedures were deemed successful if all criteria were met (Figure 16.20 and Video 16.3). The study demonstrated TVF was significantly lower in the IVUS-guided group (4.2% vs 5.4%, HR: 0.530; 95% CI, 0.312–0.901; $P = .019$). The difference between the groups was primarily driven by reduction in TVR and stent thrombosis events. Within the IVUS-guided arm, there was a dramatic reduction in TVF among those in whom all optimal criteria were met versus those in whom the criteria were not met (1.6% vs 4.4%; HR, 0.349; 95% CI, 0.135–0.898; $P = .029$) (Figure 16.21).⁸²

Both IVUS-XPL and ULTIMATE trials continued follow-up beyond the primary endpoint window of 12 months.

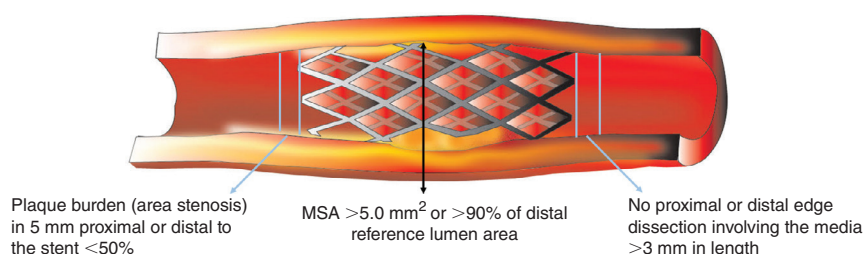


FIGURE 16.20 Criteria for optimal stent deployment from the ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in All-Coroner Coronary Lesions) trial. The prespecified criteria were set to include the need to achieve a minimum stent area in absolute terms (cutoff, 5.5 mm²) or relative terms (>90% of distal lumen reference), as well as significant attention to the reference segments (5 mm proximal and distal to the stent edges). The aims were to avoid significant disease in the references and ensure there was no significant edge dissection left behind. MSA, Minimum stent area. (From Zhang J, Gao X, Kan J, et al. Intravascular Ultrasound Versus Angiography-Guided Drug-Eluting Stent Implantation: the ULTIMATE trial. *J Am Coll Cardiol*. 2018;72: 3138-3141.)

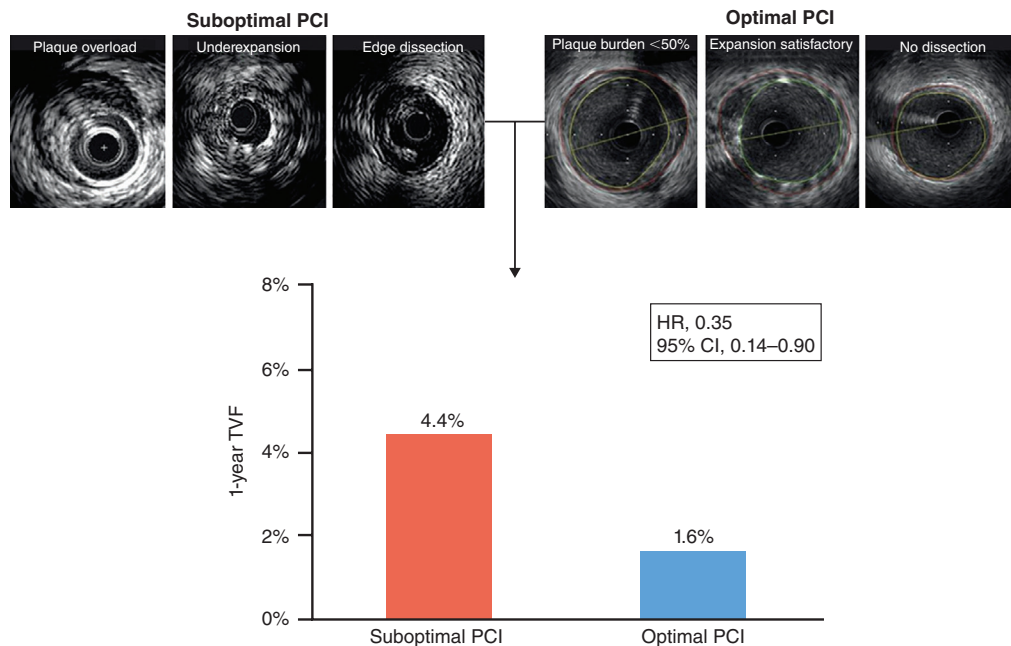


FIGURE 16.21 Impact of achieving optimal stenting criteria on target vessel failure. Within the intravascular ultrasound (IVUS) guidance group in the ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in All-Comers Coronary Lesions) trial, there was a significant difference in target vessel failure (TVF) between those in whom the optimal criteria were achieved versus those in whom that was not feasible. The *top panels* show examples of optimal versus suboptimal percutaneous coronary intervention criteria results by IVUS. The *bar graph* demonstrates the significant difference in TVF. *CI*, Confidence interval; *HR*, hazard ratio; *PCI*, percutaneous coronary intervention. (From Zhang J, Gao X, Kan J, et al. Intravascular Ultrasound Versus Angiography-Guided Drug-Eluting Stent Implantation: the ULTIMATE trial. *J Am Coll Cardiol*. 2018;72: 3138-3141.)

IVUS-XPL demonstrated persistence of the improved outcomes in the IVUS-guided arm at 5 years. The difference was primarily driven by TLR (31 [4.8%] vs 55 [8.4%]; HR, 0.54; 95% CI, 0.33–0.89; $P = .007$). Interestingly, event rates beyond the first year continued to be significantly lower in the IVUS-guided arm.⁸³ The ULTIMATE trial investigators reported the 3-year follow-up of that study, also showing maintenance of the benefit seen of IVUS guidance. That was primarily driven by significant differences in TVR and stent thrombosis, though the differences beyond the first year were not as pronounced.⁸⁴

A recent meta-analysis of 10 randomized trials including more than 5000 patients demonstrated that compared with angiography-guided PCI, IVUS guidance in the DES era resulted in a significantly lower rate of MACEs, including cardiac death, MI, TLR, and stent thrombosis at 14 months.⁸⁵ A pooled analysis of the long lesions in both IVUS-XPL and ULTIMATE (>2500 patients) demonstrated that IVUS guidance was associated with a reduction in cardiac death, as well as other ischemic endpoints, at 3 years. Interestingly, the analysis demonstrated that achievement of the ULTIMATE optimal stenting IVUS criteria was associated with statistically significant reduction in cardiac mortality compared with those with IVUS guidance but in whom optimal criteria were not achieved.⁸⁶

A more recent randomized controlled trial sought to investigate whether advanced imaging (IVUS or OCT) vs. angiography-guided PCI in complex lesions can result in improved clinical outcomes. The RENOVATE-COMPLEX-PCI (The Randomized Controlled Trial of Intravascular Imaging Guidance versus Angiography-Guidance on Clinical Outcomes after Complex Percutaneous Coronary Intervention) defined a complex lesion as one of the following:

true bifurcation lesions with a side-branch diameter of at least 2.5 mm; a chronic total occlusion; unprotected left main coronary artery disease; long lesions an expected stent length of at least 38 mm; multi-vessel PCI involving at least two major epicardial arteries being treated at the same time; a lesion that would necessitate the use of multiple stents (at least three planned stents); a lesion involving in-stent restenosis; a severely calcified lesion; or ostial lesions of a major epicardial artery. The study randomized 1639 patients in a 2:1 fashion; 1092 intravascular imaging and 547 angiography guided PCI. IVUS was the imaging modality in 73% of patients randomized to intravascular imaging. The primary end point was target-vessel failure (a composite of cardiac death, target-vessel-related myocardial infarction, or clinically driven target-vessel revascularization. Median follow up was 2.1 years. There was a statistically significant difference in favor of intravascular guidance of PCI with >25% primary endpoint reduction (7.7% vs. 12.3%, hazard ratio 0.64, CI 0.45 to 0.89; $P = 0.008$). The differences were primarily driven by reduction in target vessel related MI and repeat revascularization.^{86b}

Management of Stent Restenosis

Intravascular ultrasound imaging has provided an important perspective to study the mechanisms of restenosis after the use of various interventional devices, including stents.⁸⁷⁻⁸⁹ Unlike balloon angioplasty and stand-alone atherectomy, there is no significant recoil or negative remodeling associated with stent restenosis. True in-stent restenosis is caused by neointimal hyperplastic response that is initiated at the time of arterial wall injury caused by stent implantation. Approximately 20% of stent “restenosis”

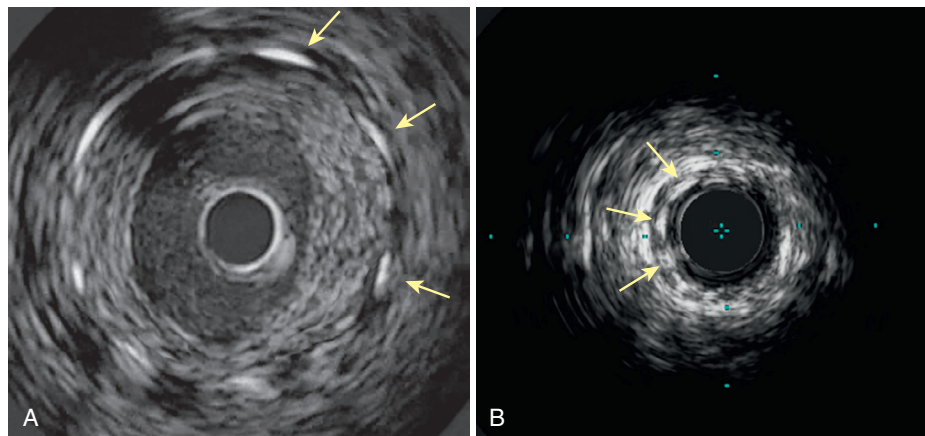


FIGURE 16.22 Mechanisms of stent restenosis. Stent lumen loss or true stent restenosis is caused by intimal hyperplasia within the boundaries of the stent struts (**A**). The originally deployed stent appears to have been well expanded. In 20% of cases of restenotic stents, the mechanism is failure to expand at the time of deployment, frequently because of undersizing or dense or calcified plaque (**B**). In these cases, neointima within the stent lumen is not the main mechanism of lumen loss, hence it can be considered “pseudo restenosis.” Arrows indicate stent struts.

results from initial underexpansion at the time of deployment, defined as a final in-stent MLA that is less than 80% of average reference lumen area (Figure 16.22).⁹⁰ Additionally, the exact localization of the restenotic site is an important variable in deciding among treatment options. If restenosis is within the stent, higher pressure inflation can be effective. Conversely, this strategy may not be appropriate to treat edge restenosis or restenosis occurring primarily in the reference segments.

When stents are adequately expanded at the time of deployment, a more conventional restenosis is caused by intimal hyperplasia within the stent struts. In such cases, restenting with DESs or brachytherapy is the available option for percutaneous therapy. Although the use of debulking devices (e.g., rotational atherectomy or laser ablation) makes theoretical sense in these cases, randomized trials have shown that these therapies are not superior to simple balloon angioplasty for treatment of in-stent restenosis.^{91,92} Recent data on drug-eluting balloons show that they can be

used for DES in-stent restenosis with similar efficacy as repeat DES.⁹³ In cases in which the stent was never fully expanded at time of deployment, treatment can be difficult. Further high-pressure or upsized balloon dilations based on IVUS measurements can be performed, although the initial under-expansion is usually secondary to heavy calcification or dense fibrotic plaques, which may not yield to balloon dilation. This may be an emerging application of intravascular lithotripsy, in which the energy waves disrupting the underlying calcium are not affected by the stent struts.⁹⁴

Assessment of Complications After Intervention

Coronary dissection is the most common cause of acute arterial closure during PCI and can result in MI or the need for emergency bypass surgery. IVUS is more sensitive in detection of dissections than angiography and can localize the extension of dissection in the arterial wall more accurately (Figure 16.23 and Video 16.4).

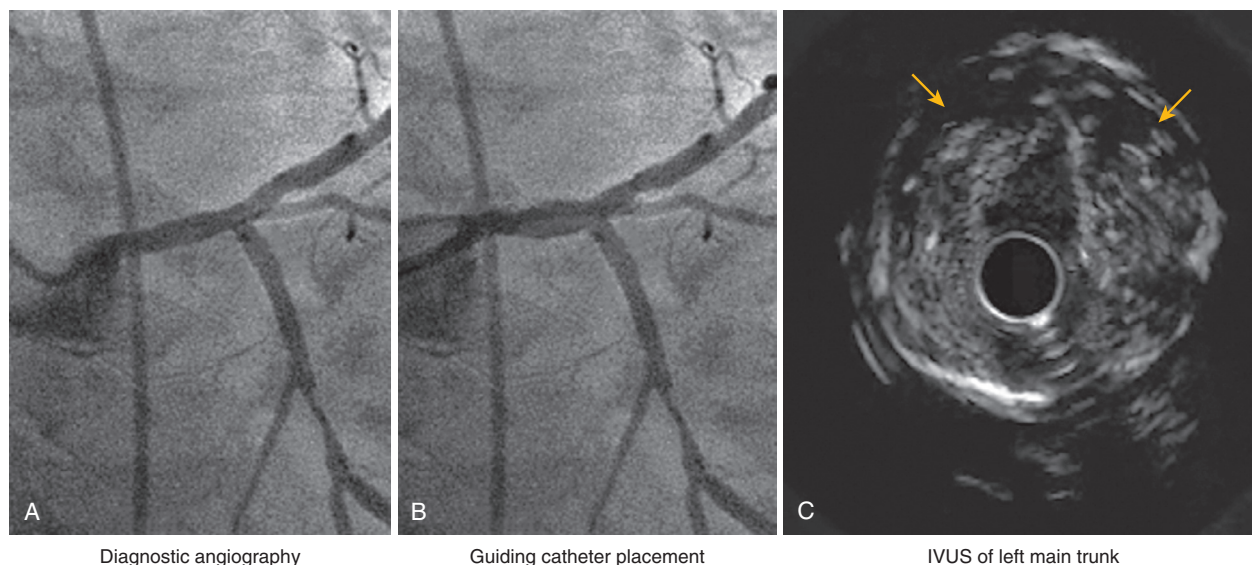


FIGURE 16.23 Role of intravascular ultrasound (IVUS) imaging in delineating procedural complications. After obtaining diagnostic angiograms (**A**), left circumflex intervention is planned. Minimal diffuse disease of the left main trunk and anterior descending artery is noted. After guide catheter engagement (**B**), the following angiograms reveal haziness and an “increase in size” of the left main trunk. IVUS imaging (**C**) delineates an extensive dissection, compromise of the lumen, and a developing intramural hematoma (arrows).

An IVUS classification of dissections is primarily based on the depth of the dissection (i.e., intimal, medial, or extending to the adventitia).¹⁰ IVUS imaging is also helpful in identifying intramural hematoma that may accompany a dissection. However, the prognosis and treatment of an intramural hematoma after intervention remain largely unknown.⁹⁵ Although the axial and circumferential extent of dissections can be better characterized on IVUS imaging, the prognostic value of IVUS findings remains unclear. Most non-flow-limiting dissections without high-risk features (i.e., persistence of contrast and spiral dissections) can be treated conservatively without additional mechanical interventions. Whenever stenting is indicated for an edge dissection, ultrasound imaging often reveals the involvement of a longer segment than can be appreciated angiographically.

This is particularly relevant in cases of bailout stenting for threatened abrupt closure, in which it is critical to cover the entire length of the dissected segment. In such cases, a residual dissection in the vicinity of the bailout stent(s) adds to the already higher risk of stent thrombosis.⁹⁶

Angiographic “haziness” after stenting is used to describe the nonhomogenous density or “ground-glass” appearance that is seen in the stent reference segment. Frequently, haziness is subtle, and angiography does not reveal a clear cause. The incidence of persistent haziness without an obvious cause has been reported to be 15% with high-pressure stenting. The main causes usually revealed on IVUS imaging are edge dissections or significant step-down of luminal area from the edge of the stent to a moderately diseased reference segment (Figures 16.24 and 16.25).⁹⁷

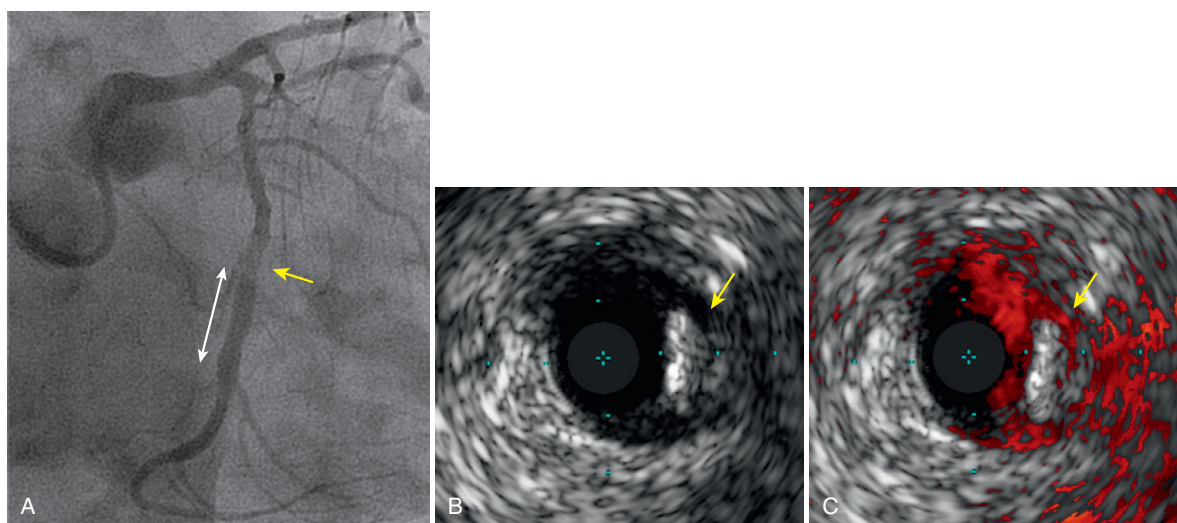


FIGURE 16.24 Persistent haziness. After stent deployment in the mid circumflex artery (**A**, white arrow), an area of angiographic haziness was noted in the proximal reference segment (yellow arrow). The stent appears slightly oversized. Grayscale intravascular ultrasound imaging (**B**) demonstrates significant disease in the reference with a small lumen. In addition, intraluminal speckle appears to extend behind an intimal flap (arrow), diagnostic of an edge dissection. Confirmation is obtained by ChromaFlo (**C**) in which color flow is seen behind the intimal flap (arrow). An additional stent was placed proximal to and overlapping with the first stent to cover the dissected segment.

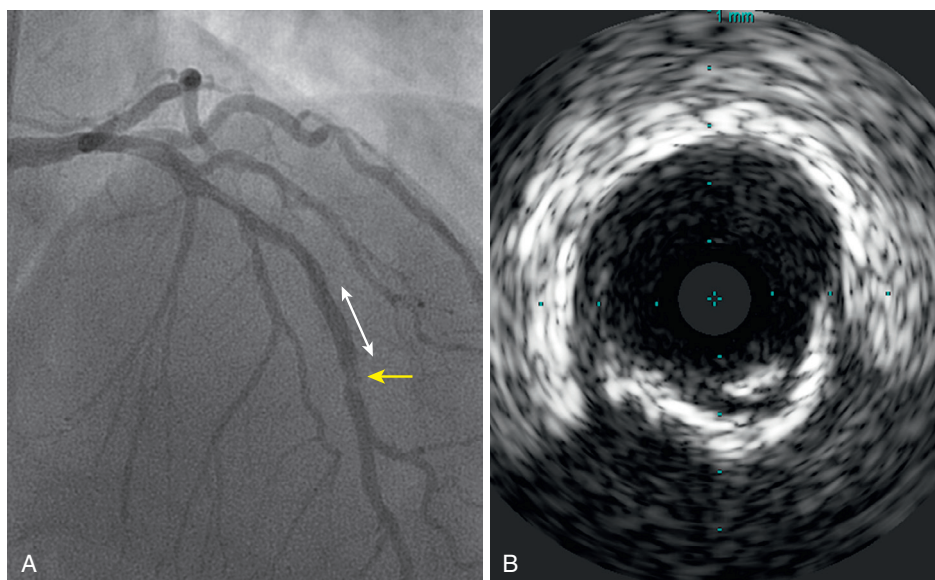


FIGURE 16.25 Persistent haziness. After stent deployment in the mid anterior descending artery (**A**, white arrow), an area of angiographic haziness was noted in the distal reference segment (yellow arrow). Intravascular ultrasound imaging (**B**) demonstrates significant and eccentric calcification in the reference vessel but with adequate lumen size and no evidence of disruption. No further intervention was deemed necessary.

Ultrasound imaging is not particularly accurate in delineation of intraluminal thrombus. These usually appear as echodense filling defects within the lumen. Mural thrombi cannot be distinguished from underlying plaque or tissue prolapse within the stent lumen because of suboptimal tissue characterization. The increasing use of higher definition IVUS probes may result in improved resolution and potential identification of thrombus layering over plaque, although the clinical context is typically needed to make such a diagnosis.

Advanced Applications of Intravascular Ultrasound Imaging in Chronic Total Occlusion Angioplasty

Angioplasty for CTO cases has recently been gaining momentum as newer techniques have improved procedural success rates and DES reduced subsequent restenosis. IVUS imaging can facilitate certain steps of a usually long and complicated procedure. To date, there are no controlled data to support these advanced applications, but IVUS imaging during CTO PCI procedures is supported by reports from experienced operators performing relatively pioneering work.

One frequently used application of IVUS imaging in CTO cases is accurate vessel sizing. After crossing the occluded segment and because of diffuse disease and chronic

underfilling, the distal vessel commonly appears smaller on angiography than its true size. IVUS imaging can delineate the burden of diffuse disease and allow the selection of a larger more appropriately sized stent, which in turn can reduce the risk of restenosis.

Other applications of IVUS in CTO cases are more complex. For example, IVUS can be used to define the location of the occluded artery when the CTO is “stumpless” or has a vague stump on angiography.⁹⁸ This can be performed if the occlusion is in the proximity of a small branch or if the occlusion is at the ostium of a coronary artery. The IVUS catheter is advanced into the patent branch, and a slow pullback is performed until the location of the occluded vessel is identified as a sector interruption of the wall, as typically seen at bifurcation points. The location is marked by filming the transducer on cine angiography. The IVUS transducer can be left in place to guide the passage of the wire into the occluded branch and can eventually help determine whether the wire is in the true lumen of the CTO by examining the wire location in the far field (Figure 16.26 and Video 16.5).

Another valuable application of IVUS imaging is to identify the true from false channels after a wire is passed through a CTO segment. If the catheter is advanced over the wire in the true lumen, the trilaminar appearance of the wall should be recognizable, and on pullback, the

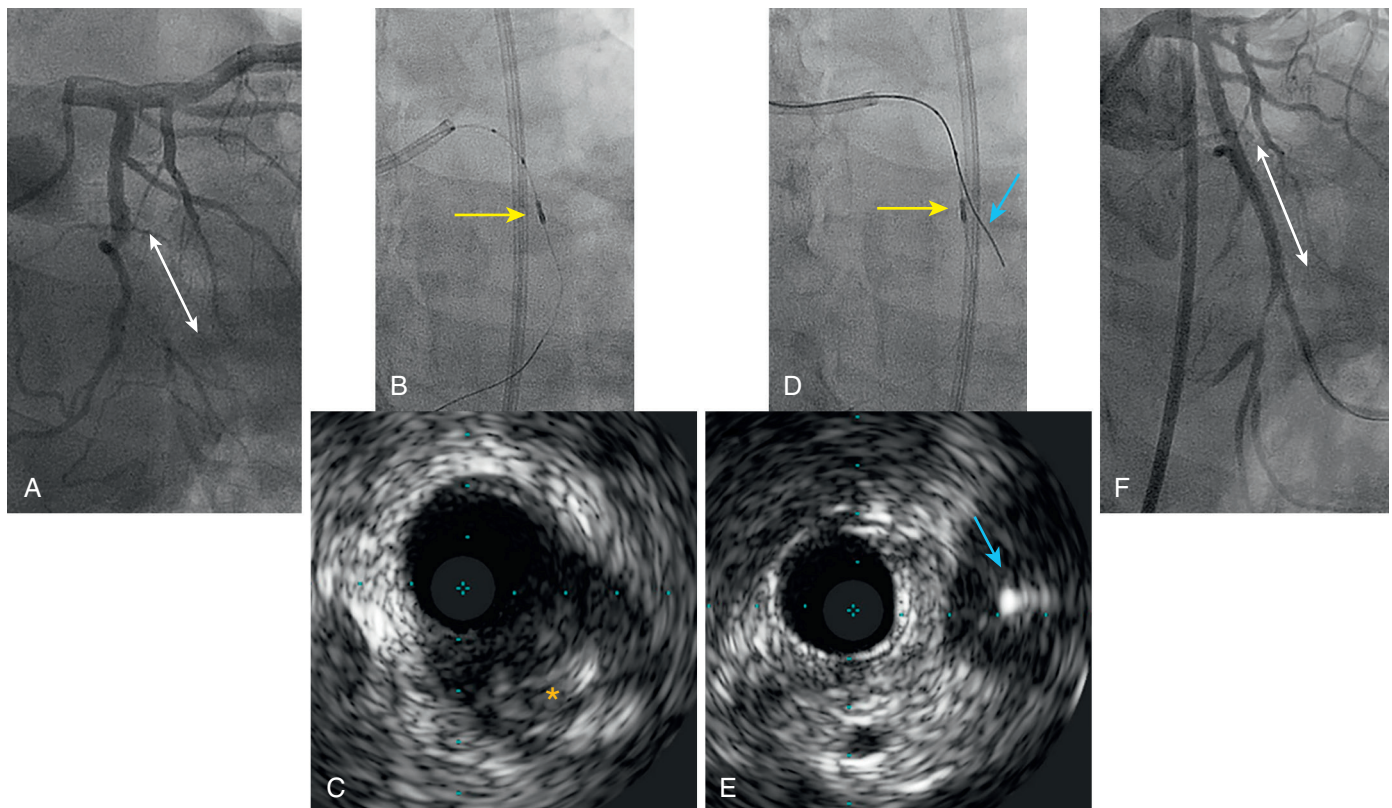


FIGURE 16.26 Use of intravascular ultrasound (IVUS) imaging in locating an occluded ostium. **A**, Angiogram of a chronically occluded marginal branch of the circumflex artery with collateral filling of the distal segment. The proximal stump of the occluded artery cannot be visualized in multiple projections. **B**, The IVUS catheter (yellow arrow) is advanced into the atrioventricular (AV) continuation of the artery and pulled back until the bifurcation of the occluded marginal branch is visualized (asterisk, **C**). The location of the stump is marked on cineangiography and a stiff wire (blue arrow) is advanced through the proximal cap of the occlusion (**D**). The entry of the wire into the marginal branch and confirmation of its intraluminal position is confirmed by keeping the IVUS probe in place and focusing on the wire artifact in the far field (blue arrow, **E**). After crossing, balloon angioplasty and stenting of the occluded segment are successfully performed (white arrow, **F**).

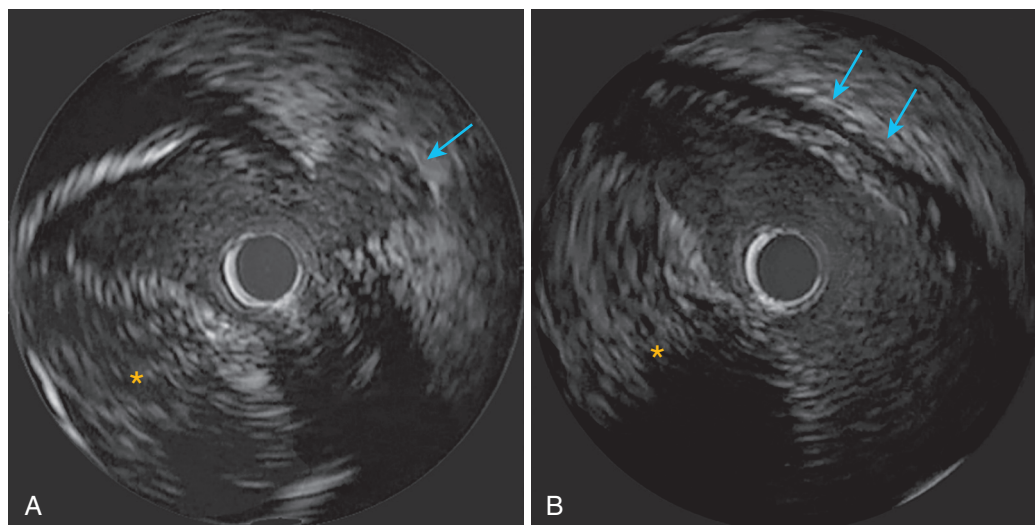


FIGURE 16.27 Distinguishing between true and false lumens. In complex interventions, particularly chronic total occlusion percutaneous coronary intervention, it is crucial to define the true lumen before proceeding with angioplasty and stenting. Advancing an intravascular ultrasound (IVUS) probe can provide two useful clues to distinguish between true and false lumens: branches always originate from true lumen (arrow, **A**), and the trilaminar appearance of the wall can only be present in a non-dissected lumen (arrows, **B**). In this example, the IVUS catheter is in the true lumen and is separated from the false channel (asterisk) by a linear echodensity, which represents the dissection flap.

orifices of side branches are seen. In a false channel, the wall is not trilaminar, and the side branches may be seen arising from the lumen separated from the catheter by the linear echodensity of the dissection flap (Figure 16.27). Lower profile IVUS catheters have been used for this application in Asia and Europe. If the catheter is determined to be in a false channel, it can help guide the passage of a second wire into the true lumen, which can be seen in the far field.⁹⁹ This application can be performed via the retrograde and antegrade techniques and has proven valuable in salvaging procedures in which the true lumen could not be identified angiographically.¹⁰⁰

INTRAVASCULAR ULTRASOUND IMAGING IN THE PERIPHERAL ARTERIAL SYSTEM

As with some other advanced applications, there are no guideline-based recommendations for use of IVUS imaging in the peripheral vasculature. The applications are driven by need for additional information not accurately provided by angiography alone. Technically, imaging of larger arteries requires deeper penetration, which in turn means imaging at a lower frequency, typically 10 to 20 MHz. Peripheral imaging catheters are larger and can be advanced over 0.018 or 0.035-inch wires. Coronary imaging catheters can be used in the peripheral arteries that are 3 to 5 mm in diameter. IVUS imaging of peripheral arteries is not new. Some of the early validation studies were performed on femoral artery sections,¹³ and many of the pioneering work in understanding remodeling in vivo was also done in peripheral arteries.^{101,102} More recently, comparative studies demonstrated accuracy of IVUS in obtaining accurate lumen measurements and its superiority in defining plaque and calcification distribution in comparison with subtraction angiography.¹⁰³

A simple application of IVUS in the peripheral arteries is accurate vessel sizing. This is important for device selection

during atherectomy, balloon angioplasty, or for stent sizing. An important contemporary use of IVUS imaging is the sizing of the iliac artery before transfemoral transcatheter aortic valve replacement. With the large size of the delivery system, it is critically important to define the size of the artery, distribution of plaque burden, and extent of calcification. Typically, this is done using contrast CT imaging or angiography, but IVUS imaging can provide similar or more accurate information without the use of contrast, which can be valuable in older adult patients with moderate degrees of renal insufficiency (Figure 16.28).¹⁰⁴

Intravascular ultrasound imaging is also valuable to guide endovascular repair of abdominal aortic aneurysms. Several measurements and morphologic information are important to delineate during such procedures. Diameter, length, branch vessels, and plaque distribution of the infrarenal neck of the aneurysm are important for accurate anchoring of the graft. Similar information can be obtained about the distal landing zone in the iliac artery. Imaging can also be used to define complications at the landing zones if the angiograms are ambiguous. Importantly, this information can be obtained with minimal contrast and without excessive radiation exposure.¹⁰⁵

As previously described with CTO PCI, IVUS imaging from within the subintimal space can guide reentry into the true lumen and facilitate restoration of flow in cases in which antegrade access to the true lumen is not directly feasible. This technique is used in the femoral, popliteal, and iliac arteries as well. For this application, a dedicated 6-Fr dual-lumen IVUS catheter is equipped with a phased-array transducer and a deployable needle at its tip. After wire access has been gained into the subintimal space at the proximal cap, the dissection is extended along the length of the occluded segment. The catheter is then advanced over a wire placed in the subintimal space. When the transducer reaches the level of the distal cap, the true lumen can be identified in the far field. The IVUS catheter

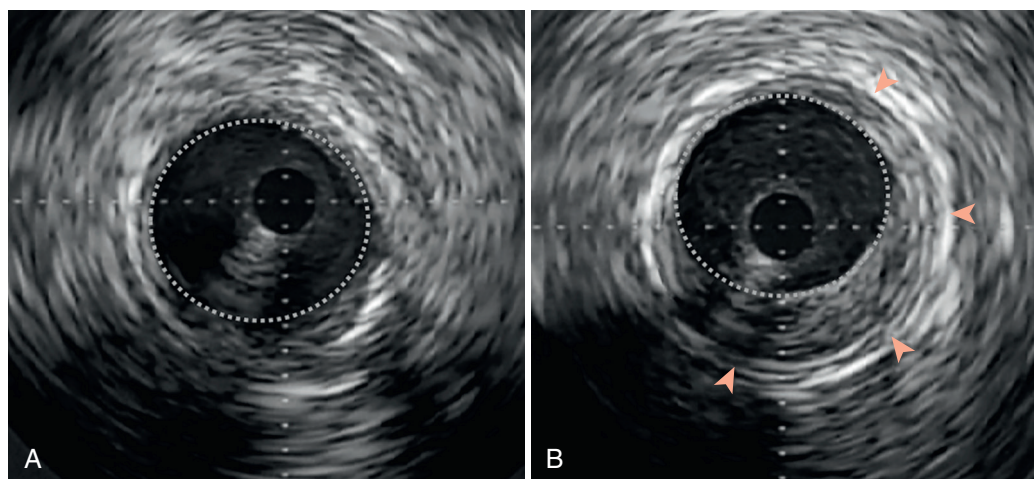


FIGURE 16.28 Intravascular ultrasound (IVUS) imaging of the iliac arteries. Peripheral IVUS imaging can provide accurate measurements of the iliac arteries and the aorta for interventional planning. To visualize the wall of the larger arteries from the center of the lumen, a lower frequency ultrasound is needed, typically 10 to 20 MHz. This lowers the resolution, which can be seen as less definition of the arterial wall components. Additionally, the iliac arteries are less muscular than the coronaries, so the media is thinner and harder to visualize. **A**, A near-normal iliac artery with mild intimal thickening. **B**, A more distal segment with early disease seen as an eccentric plaque (*arrowheads*). This is an example of positive remodeling, as the lumen size (bound by the *dotted gray border*) remained unchanged with development of atherosclerotic plaque in the distal vessel.

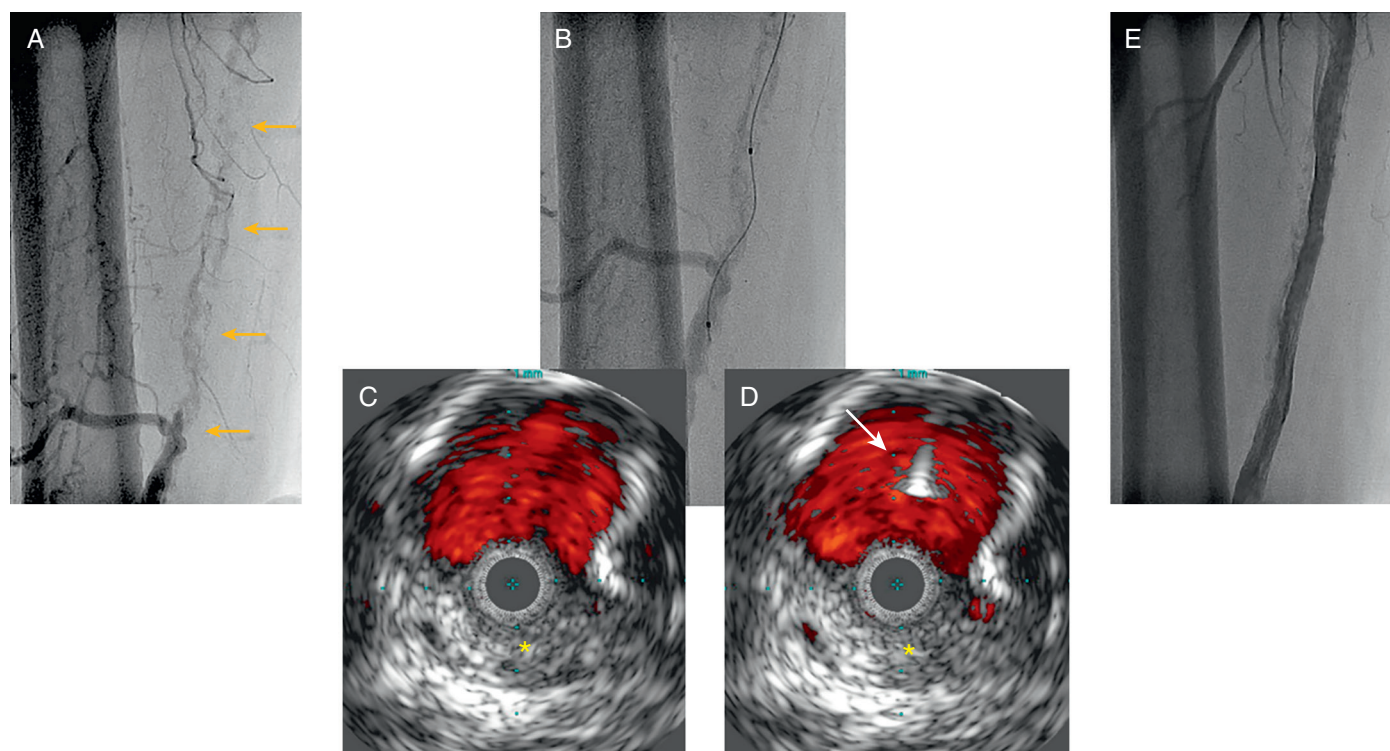


FIGURE 16.29 Use of intravascular ultrasound (IVUS) imaging to facilitate reentry in subintimal angioplasty of the femoral artery. **A**, An angiogram of a long and calcified superficial femoral artery occlusion (*arrows*) with reconstitution via collaterals from the profunda femoris artery. **B**, A stiff wire is used to penetrate the proximal cap and dissect the wall to create a subintimal track extending all the way to the distal stump. **C**, The dedicated reentry IVUS catheter is then delivered into the subintimal space (*asterisk*) until it reaches the level of the distal stump. **D**, The true channel is then visualized with the aid of ChromaFlo. **E**, After appropriate positioning, the needle is used for reentry, and the angioplasty wire is advanced in the distal true lumen (*arrow*). **F**, Balloon angioplasty and a self-expanding stent follow to restore patency.

is rotated appropriately, such that the needle penetrates the intimal flap into the true lumen when deployed. After this is achieved, an angioplasty wire can be advanced via the deployed needle to gain reentry into the true lumen (Figure 16.29 and Video 16.6). This technique facilitates difficult CTO cases with calcified caps and long occluded segments, saves contrast and radiation exposure, and improves success rates.¹⁰⁶

RESEARCH APPLICATIONS: PROGRESSION AND REGRESSION TRIALS

In addition to its value as a clinical tool to facilitate diagnosis of and interventions in catheterization laboratories, IVUS imaging has been a very valuable tool to gain insight into the atherosclerotic disease process. IVUS imaging was the first imaging modality used to demonstrate the



process of arterial remodeling in vivo and its potential interaction with the propensity for plaque rupture and development of clinical events.^{8,107} It has also been used to study the impact of various therapeutic agents on progression and regression of atherosclerosis. The tested therapies included statins, antidiabetic agents, and renin-angiotensin system inhibitors. Such trials attempted to establish a new standard for the evaluation of drug therapy to limit the progression of atherosclerosis. To avoid variability in measured endpoints and to allow for comparison across trials, a consensus document outlined the most accepted methods of image acquisition, measurement, and endpoint reporting in studies of disease progression.¹⁰⁸ The serial studies that are essential for such studies require a high level of expertise during image acquisition and analysis. Volumetric quantification of the atheroma volumes is used to reduce variability. A number of endpoints are suggested in this document, although percent atheroma volume (PAV) has been the most commonly reported.

A larger study of 654 patients sought to use serial IVUS imaging to examine the effect of intensive (atorvastatin 80 mg) versus standard (pravastatin 40 mg) lipid-lowering therapy on coronary atherosclerosis.¹⁰⁹ IVUS imaging was performed at baseline and after 18 months of therapy. As expected, low-density lipoprotein (LDL) cholesterol was significantly lower in the high-dose statin arm, but the change in PAV was minimal compared with baseline (-0.4%; $P = .98$ compared with baseline). In the pravastatin arm, there was significant progression in PAV (+2.7%; $P = .001$ compared with baseline). The difference between the groups was statistically significant in this primary endpoint as well as other secondary measures of disease progression. Subsequently, in a cohort treated with rosuvastatin to achieve more aggressive reduction of LDL cholesterol and using historic control group, rosuvastatin therapy was associated with a measurable regression in plaque size. With intense lipid lowering, the mean and median changes in PAV for the entire vessel were -0.98% and -0.79%, respectively ($P < .001$ vs baseline).¹¹⁰

Although the absolute reduction in atheroma burden as measured by IVUS in each of these trials was small, its clinical significance remains unclear. Minimal progression may be a marker for arteries with more “active” disease or patients more susceptible to events. In an analysis of 4137 patients from six clinical trials that used serial IVUS to study plaque progression, there was a significant association between baseline disease burden and major adverse events, such that every standard deviation increase in PAV was associated with a 1.32-fold (95% CI, 1.22–1.42; $P < .001$) greater likelihood of experiencing an adverse event. Similarly, disease progression over the 2 years of follow-up was another predictor of adverse events: each standard deviation greater increase in PAV was associated with a 1.20-fold (95% CI, 1.10–1.31; $P < .001$) greater risk for adverse events.¹¹¹

ADVANCING INTRAVASCULAR ULTRASOUND TECHNOLOGIES AND FUTURE DIRECTIONS

Over the past 2 decades, there has been growing interest in better understanding of plaque composition and its role

in defining plaque vulnerability. Using grayscale IVUS imaging for tissue characterization has modest accuracy. In addition, resolution of IVUS is limited and may not allow detection of features considered essential to the diagnosis of plaque vulnerability. This led to the introduction of an advanced ultrasound-based tissue characterization technology, virtual histology (VH). IVUS tomography has also been combined with other tissue characterization techniques such as near-infrared spectroscopy (NIRS). Other innovations to overcome limitations of current IVUS imaging include the development of high-definition imaging using 60-MHz transducers and the development of hybrid IVUS–OCT imaging catheters.

Intravascular Ultrasound-Derived Virtual Histology

Intravascular ultrasound-derived VH is a more advanced imaging technique that depends on analysis of the radio-frequency backscatter of the ultrasound signal using a larger number of parameters. Rather than just using the signal amplitude to define a shade of gray for each reflected line, this method uses a more complex mathematical autoregressive model to calculate the frequency spectrum from the region of interest (the coronary plaque).¹¹² The complex mathematical calculations do not lend themselves to quick interpretations by clinicians, hence the development of a simplified color-coded display that broadly distinguishes lipidic, fibrotic, necrotic, and calcific regions (Figure 16.30). This approach to analysis of the IVUS data can allow the identification of the thin-cap fibroatheroma (TCFA), considered by many pathologists to be the plaque most prone to rupture and cause acute clinical events. TCFA is defined as a lipid-rich plaque (>10% confluent lipid core) with a very thin cap (<100 μm in thickness, not visible by VH) and with an area stenosis that is usually larger than 40%. These plaques frequently contain speckles of calcification and are more prevalent in patients presenting with ACSs, even in nonculprit segments (Figure 16.31). TCFA is most frequently located in proximal coronary arterial segments, which is consistent with the patterns of angiographic lesions underlying acute MI.¹¹³ It is important to note that in calcified plaques, the poor penetration of ultrasound signals through the calcium affects the accuracy of the backscatter interpretation. In such cases, the attenuation caused by the calcified plaque is interpreted as necrotic core, thus artifactually overestimating its measured area by VH IVUS.¹¹⁴ Other plaque imaging modalities are more accurate in defining the size of the lipid core in calcified plaques (e.g., NIRS).¹¹⁵

The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial is the largest study to date that provides insight into the natural history of various types of atherosclerotic plaque as defined by VH IVUS.¹¹⁶ In this study, 697 patients with ACSs entered into a registry with longitudinal follow-up. All underwent angiography and revascularization as clinically indicated. Three vessel IVUS imaging and VH analysis were performed. Patients who developed events over the ensuing 3 years underwent repeat angiography and imaging.

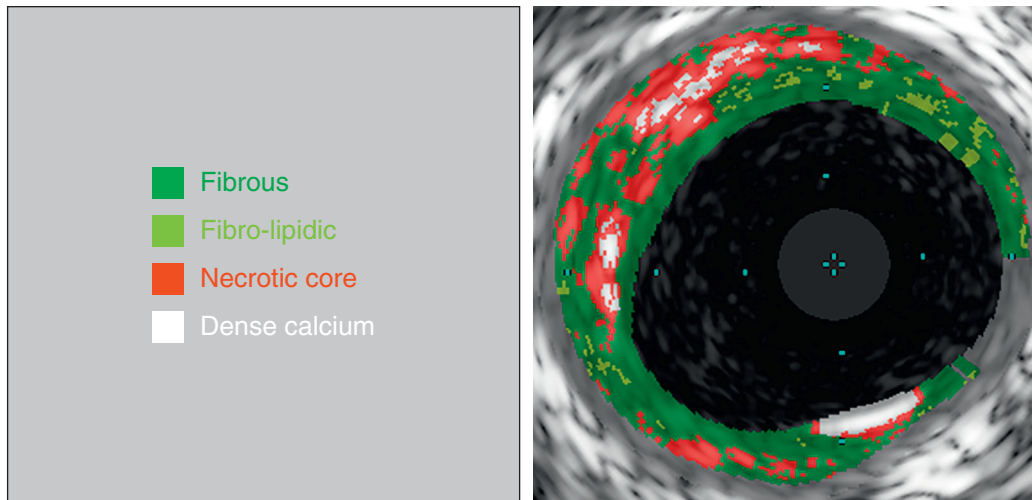


FIGURE 16.30 Virtual histology intravascular ultrasound imaging. Using radiofrequency backscatter analysis, the variable components of the plaque (e.g., lipid, fibrous tissue, and calcium) can be identified. The display is then color coded, and an online evaluation of plaque structure can be available to the operator. (From Nair A, Kuban BD, Tuzcu EM, et al. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. *Circulation*. 2002;106:2200-2206.)

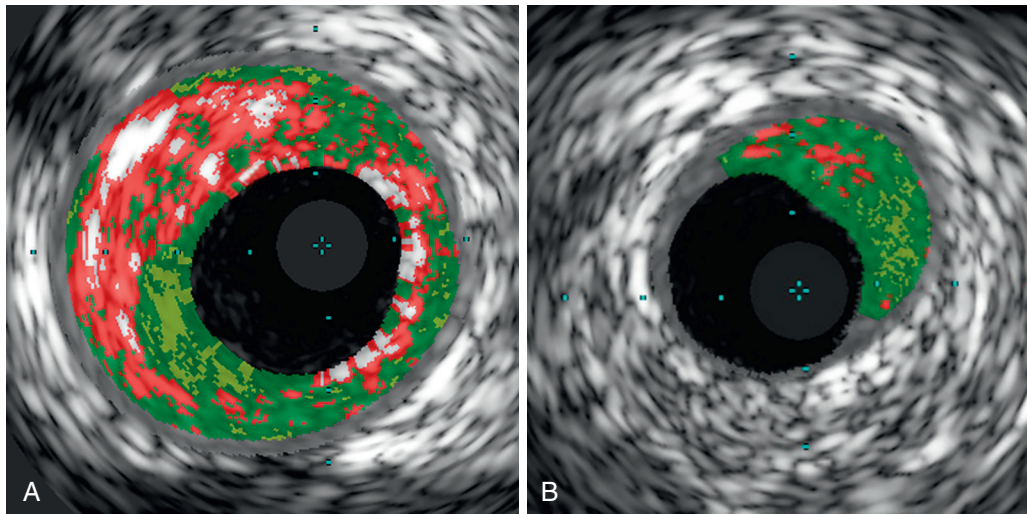


FIGURE 16.31 Examples of virtual histology (VH) intravascular ultrasound (IVUS) imaging and plaque composition. **A**, A thin cap fibroatheroma (TCFA) as defined on VH IVUS imaging: a lipid-rich plaque with a larger than 10% confluent necrotic core, a very thin cap that is less than 100 μm in thickness (hence not visible by VH leading to direct proximity between the necrotic core and the lumen), and more than 40% cross-sectional area stenosis. These plaques are more likely seen in the context of acute coronary syndromes. **B**, A fibrous plaque with minimal necrotic core and one that is more likely seen in patients with stable coronary disease.

Adverse events were related to an originally nonculprit lesion in 11.6% of patients. Lesion characteristics that predicted development of future events included plaque burden 70% or greater, MLA 4 mm^2 or less, and TCFA on VH IVUS. The presence of more than one feature increased the risk of future events.

Intravascular Ultrasound and Near-Infrared Spectroscopy

Interest in identification of plaque vulnerability and recognition of the importance of the lipid core underlie the development of NIRS-equipped catheters. NIRS is a technology widely used to detect the chemical content of

substances and can be used to detect lipid content with satisfactory accuracy.¹¹⁷ A currently available combined NIRS IVUS catheter provides simultaneous NIRS spectral data co-registered with traditional IVUS images in a single intracoronary pullback. This allows the recognition of lipid cores within the plaque and the morphometric features (e.g., area, volume, and distribution), both characteristics that can predict vulnerability¹¹⁸ (Figure 16.32). A large prospective cohort trial followed more than 1200 patients in whom nonculprit lesions were imaged using NIRS IVUS. Plaque lipid content was assessed using the 4 mm with maximum lipid core burden index ($\text{maxLCBI}_{4\text{mm}}$). On a patient level, the hazard of developing MACE over 2 years because of the imaged nonculprit lesion significantly

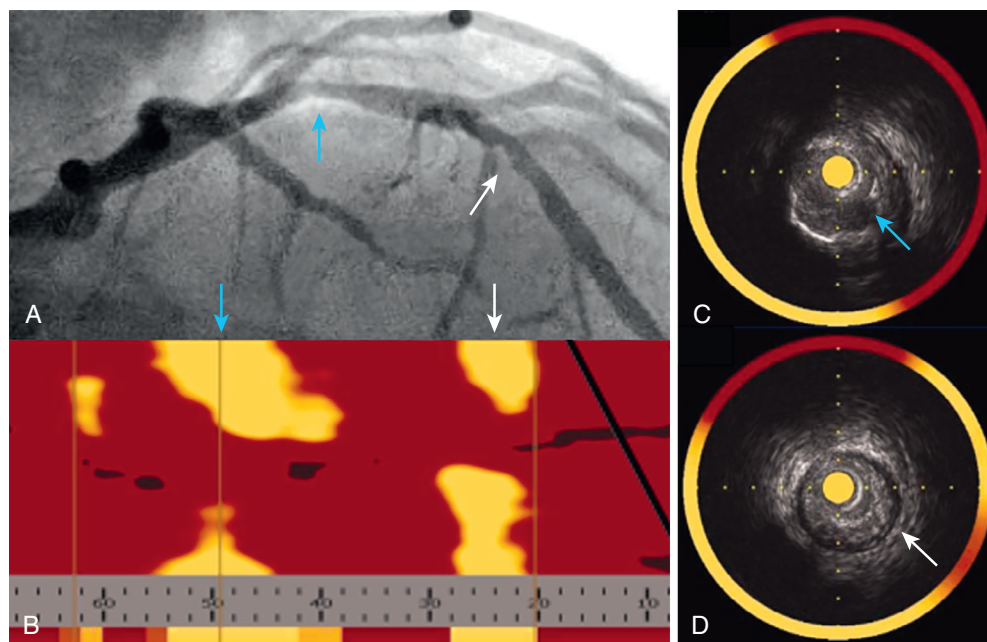


FIGURE 16.32 The combination of intravascular ultrasound (IVUS) and near-infrared spectroscopy (NIRS) in coronary imaging. An example of the value of multimodality imaging for detection of plaque vulnerability or activity. **A**, An angiogram of the left anterior descending coronary artery (LAD) reveals a proximal hazy lesion (white arrow) that is considered the culprit underlying the acute presentation. There is a midsegment lesion that appears mild in severity (blue arrow). **B**, The chemogram generated by NIRS imaging reveals evidence of large lipid content in the proximal lesion (white arrow) but also in the midsegment lesion (blue arrow). IVUS imaging confirms signs of plaque rupture and ulceration in the proximal lesion (**C**, blue arrow). The less severe lesion in the midsegment did show evidence of large lipid core (white arrow on chemogram) and IVUS revealed a larger than expected plaque burden (**D**, white arrow). (From Madder RD, Steinberg DH, Anderson RD. Multimodality direct coronary imaging with combined near-Infrared spectroscopy and intravascular ultrasound: initial US experience. *Catheter Cardiovasc Interv*. 2013;81:551-557.)

increased when maxLCBI4mm increased (semiquantitatively and by using a cutoff of 400). Similar observations were made when analysis was performed on a plaque level.¹¹⁹

High-Definition Imaging

A high-definition 60-MHz IVUS catheter system has been developed to potentially bridge the image resolution gap between IVUS and OCT imaging. The challenge to develop a higher resolution transducer without affecting depth of penetration seems to have been overcome in this new device.¹²⁰ Preliminary data demonstrate significantly improved resolution compared with contemporary 40- to 45-MHz transducers and image quality comparable to that acquired by OCT¹²¹ (Figure 16.33). Forward-looking transducers are also being developed to allow guidance of interventions in occluded vessels. Using advanced imaging suites in which IVUS imaging pullbacks can be co-registered in three dimensions with biplane angiography will also allow depiction of coronary trees that can be used in calculation of shear stress, another important predictor of cardiac events.

Novel hybrid catheters allowing both IVUS and OCT imaging has been developed. Different technical approaches were used to house the OCT light source and the IVUS transducer in the catheter while keeping the size of the catheter, but animal and human cadaveric studies have demonstrated good image quality. Importantly, the IVUS and OCT images can be co-registered, allowing detailed examination of the arterial wall, leveraging both modalities simultaneously. One catheter (Novasight Hybrid System, Conavi Medical) has received preliminary US Food

and Drug Administration clearance and is approved for use in Canada. The other (Dual Sensor, Teromu) is close to commercial application. The Dual Sensor catheter specifications are very similar to current IVUS catheters and the imaging system operates in a very similar fashion as well. Examples of acquired images from cadaveric coronary arteries are shown in Figure 16.34.¹²²

Intravascular Ultrasound and Optical Coherence Tomography Imaging

With the availability of catheter-based OCT imaging, the question of which IVI modality is more useful for the interventionalist is being considered. It is clear that both modalities provide additive insight over angiography alone in many diagnostic and interventional applications. The judicious use of either modality is likely to answer a question or a concern that is not clearly resolved by angiographic examination. Nonetheless, each modality has its own advantages and disadvantages.^{123,124}

There is little debate that the higher resolution of OCT provides significant advantages over IVUS imaging in certain categories, namely, (1) improved spatial resolution (20–40 μm) that allows better definition of TCFA and dissection flaps and (2) diagnosis of intraluminal thrombus and (3) better definition of the depth of calcium deposits. This is typically not well identified by IVUS imaging because of the backshadow caused by the reflection of the ultrasound beam. However, there are certain advantages to IVUS imaging that remain relevant despite its lower resolution. The use of light waves in OCT imaging does not allow penetration and imaging of the full thickness of the

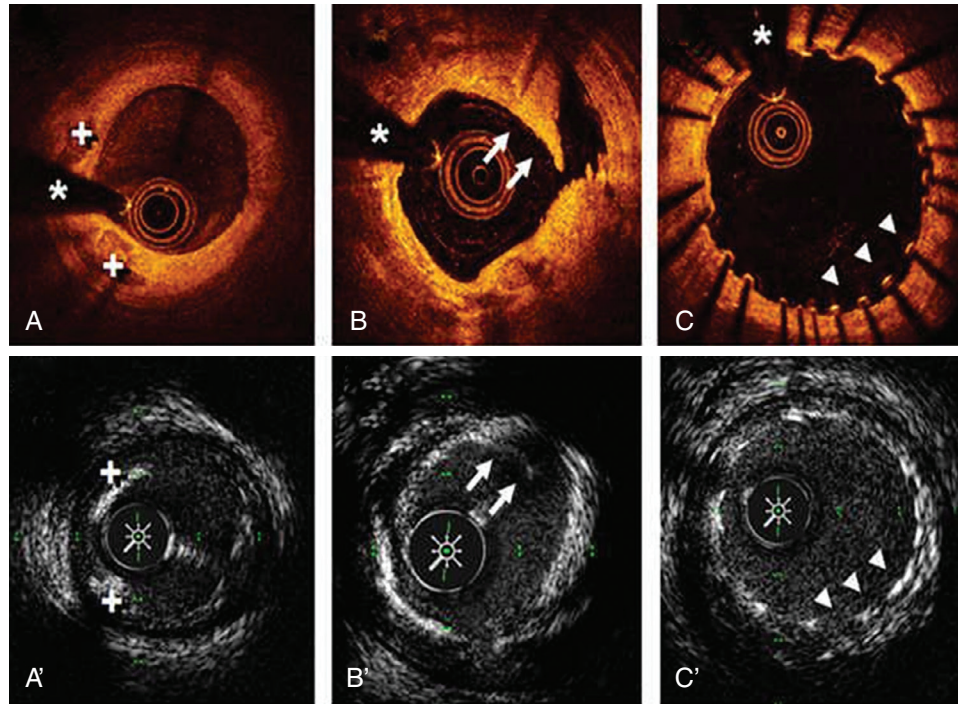


FIGURE 16.33 Improved resolution with high-definition intravascular ultrasound (IVUS) imaging. With the development of 60-Hz high-definition IVUS probes, the difference in resolution between IVUS and optical coherence tomography (OCT) can be reduced significantly. The *upper row* of images shows the OCT findings, and the *lower row* of images shows the corresponding high-definition IVUS frames. **A** and **A'** show an area of fibrocalcified plaque, in which calcified nodules are demarcated (+). **B** and **B'** show the immediate result after balloon angioplasty of a severely calcified lesion, leading to an intimal dissection flap. **C** and **C'** show drug-eluting stent struts 9 months after implantation, demonstrating the absence of strut endothelialization in two-thirds of the circumference, as well as an area of malapposition (arrowheads). (From García-Guimaraes M, Cuesta J, Rivero F, Bastante T, Benedicto A, Alfonso F. High-definition intravascular ultrasound vs optical coherence tomography: preliminary experience. *Rev Esp Cardiol.* 2018;71:119-120.)

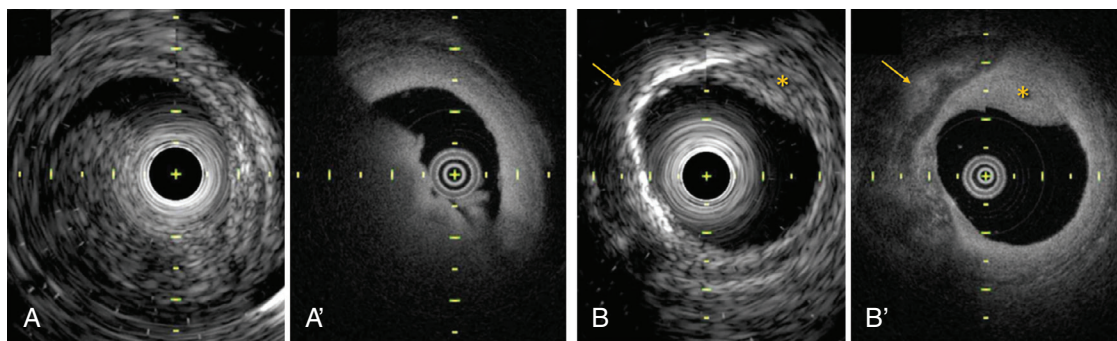


FIGURE 16.34 Hybrid imaging with optical coherence tomography (OCT) and high-definition intravascular ultrasound (IVUS) imaging. Sample images obtained by the Terumo hybrid IVUS–OCT catheter system from a cadaveric coronary artery. After acquisition using the hybrid catheter, the images are co-registered, so IVUS and OCT perspectives of each frame can be matched. An intraluminal thrombus imaged by IVUS (**A**), with the corresponding OCT image (**A'**). A heterogeneous plaque with calcification (arrow) and fibrotic elements (asterisk) by IVUS (**A**) and the corresponding OCT images (**B'**). (From Ono M, Kawashima H, Hara H, et al. Advances in IVUS/OCT and future clinical perspective of novel hybrid catheter system in coronary imaging. *Front. Cardiovasc Med.* 2020;7:119.)

arterial wall (i.e., OCT provides exquisite resolution) but only of the luminal 1 to 2 mm of the wall. Thus deeper structures that can influence strategy and result of an interventional procedure (e.g., deep calcification, dense fibrous plaques) may not be adequately visualized. Moreover, poor penetration does not allow measurement of plaque thickness and volume, measures of plaque burden that have been shown to define future risk of clinical events in the PROSPECT trial. These measurements are also essential for study of phenomena such as remodeling,

disease progression, and response to therapeutic interventions. Evidence supporting OCT imaging in diagnostic and interventional applications continue to accumulate.

ACKNOWLEDGMENT

The author would like to acknowledge Dr. Wael El Mallah for his invaluable assistance with preparation of the video examples accompanying this chapter.

REFERENCES

1. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation*. 1995;92:2333-2342.
2. Ziada KM, Kapadia SR, Tuzcu EM, Nissen SE. The current status of intravascular ultrasound imaging. *Curr Probl Cardiol*. 1999;24:541-566.
3. Zir LM, Miller SW, Dinsmore RE, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. *Circulation*. 1976;53:627-632.
4. Galbraith JE, Murphy ML, de Soya N. Coronary angiogram interpretation. Interobserver variability. *JAMA*. 1978;240:2053-2056.
5. Vlodaver Z, Frech R, Van Tassel RA, Edwards JE. Correlation of the antemortem coronary arteriogram and the postmortem specimen. *Circulation*. 1973;47:162-169.
6. Arnett EN, Isner JM, Redwood DR, et al. Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and necropsy findings. *Ann Intern Med*. 1979;91:350-356.
7. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Koletis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*. 1987;316:1371-1375.
8. Schoenhagen P, Ziada KM, Vince DG, Nissen SE, Tuzcu EM. Arterial remodeling and coronary artery disease: the concept of "dilated" versus "obstructive" coronary atherosclerosis. *J Am Coll Cardiol*. 2001;38:297-306.
9. Schoenhagen P, Ziada KM, Kapadia SR, et al. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. *Circulation*. 2000;101(6):598-603.
10. Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS) 33: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents developed in collaboration with the European Society of Cardiology endorsed by the Society of Cardiac Angiography and Interventions. *J Am Coll Cardiol*. 2001;37(5):1478-1492.
11. Raber L, Mintz GS, Koskinas KC, et al. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J*. 2018;39:3281-3300.
12. Saito Y, Kobayashi Y, Fujii K, et al. Clinical expert consensus document on intravascular ultrasound from the Japanese Association of Cardiovascular Intervention and Therapeutics (2021). *Cardiovasc Interv Ther*. 2022;37(1):40-51.
13. Gussenhoven EJ, Essed CE, Lancee CT, et al. Arterial wall characteristics determined by intravascular ultrasound imaging: an in vitro study. *J Am Coll Cardiol*. 1989;14:947-952.
14. Tuzcu EM, Berkalp B, De Franco A, et al. The dilemma of diagnosing coronary calcification: angiography versus intravascular ultrasound. *J Am Coll Cardiol*. 1996;27:832-838.
15. Mintz GS, Popma JJ, Pichard AD, et al. Patterns of calcification in coronary artery disease: a statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. *Circulation*. 1995;91:1959-1965.
16. Lee JB, Mintz GS, Lissauskas JB, et al. Histopathologic validation of the intravascular ultrasound diagnosis of calcified coronary artery nodules. *Am J Cardiol*. 2011;108(11):1547-1551.
17. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and The Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58(24):e44-e122.
18. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:e21-e129.
19. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334:1703-1708.
20. Bech GJ, De Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation*. 2001;103:2928-2934.
21. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol*. 2007;49:2105-2111.
22. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360(3):213-224.
23. Takagi A, Tsurumi Y, Ishii Y, Suzuki K, Kawana M, Kasanuki H. Clinical potential of intravascular ultrasound for physiological assessment of coronary stenosis: relationship between quantitative ultrasound tomography and pressure-derived fractional flow reserve. *Circulation*. 1999;100:250-255.
24. Briguori C, Anzuini A, Airolidi F, et al. Intravascular ultrasound criteria for the assessment of the functional significance of intermediate coronary artery stenoses and comparison with fractional flow reserve. *Am J Cardiol*. 2001;87:136-141.
25. Ben-Dor I, Torguson R, Deksis T, et al. Intravascular ultrasound lumen area parameters for assessment of physiological ischemia by fractional flow reserve in intermediate coronary artery stenosis. *Cardiovasc Revasc Med*. 2012;13(3):177-182.
26. Isner JM, Kishel J, Kent KM, Ronan JA Jr, Ross AM, Roberts WC. Accuracy of angiographic determination of left main coronary arterial narrowing. Angiographic—histologic correlative analysis in 28 patients. *Circulation*. 1981;63:1056-1064.
27. Fisher LD, Judkins MP, Lesperance J, et al. Reproducibility of coronary arteriographic reading in the coronary artery surgery study (CASS). *Cathet Cardiovasc Diagn*. 1982;8:565-575.
28. Jasti V, Ivan E, Yalamanchili V, Wongprapart N, Leesar MA. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation*. 2004;110:2831-2836.
29. Abizaid AS, Mintz GS, Abizaid A, et al. One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. *J Am Coll Cardiol*. 1999;34:707-715.
30. Fassa AA, Wagatsuma K, Higano ST, et al. Intravascular ultrasound-guided treatment for angiographically indeterminate left main coronary artery disease: a long-term follow-up study. *J Am Coll Cardiol*. 2005;45:204-211.
31. Mehra MR, Crespo-Leiro MG, Dipchand A, et al. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy—2010. *J Heart Lung Transplant*. 2010;29(7):717-727.
32. Uretsky BF, Murali S, Reddy PS, et al. Development of coronary artery disease in cardiac transplant patients receiving immunosuppressive therapy with cyclosporine and prednisone. *Circulation*. 1987;76:827-834.
33. Pascoe EA, Barnhart GR, Carter WH Jr, et al. The prevalence of cardiac allograft arteriosclerosis. *Transplantation*. 1987;44:838-839.
34. Pflugfelder PW, Boughner DR, Rudas L, Kostuk WJ. Enhanced detection of cardiac allograft arterial disease with intracoronary ultrasonographic imaging. *Am Heart J*. 1993;125:1583-1591.
35. Pinto FJ, St Goar FG, Gao SZ, et al. Immediate and one-year safety of intracoronary ultrasonic imaging. Evaluation with serial quantitative angiography. *Circulation*. 1993;88:1709-1714.
36. Ramasubbu K, Schoenhagen P, Balgith MA, et al. Repeated intravascular ultrasound imaging in cardiac transplant recipients does not accelerate transplant coronary artery disease. *J Am Coll Cardiol*. 2003;41:1739-1743.
37. Tuzcu EM, De Franco AC, Hobbs R, et al. Prevalence and distribution of transplant coronary artery disease: insights from intravascular ultrasound imaging. *J Heart Lung Transplant*. 1995;14(suppl):S202-S207.
38. Escobar A, Ventura HO, Stapleton DD, et al. Cardiac allograft vasculopathy assessed by intravascular ultrasonography and nonimmunologic risk factors. *Am J Cardiol*. 1994;74:1042-1046.
39. St Goar FG, Pinto FJ, Alderman EL, et al. Intracoronary ultrasound in cardiac transplant recipients. In vivo evidence of "angiographically silent" intimal thickening. *Circulation*. 1992;85:979-987.
40. Kapadia SR, Nissen SE, Ziada KM, et al. Development of transplantation vasculopathy and progression of donor-transmitted atherosclerosis: comparison by serial intravascular ultrasound imaging. *Circulation*. 1998;98:2672-2678.
41. Gao HZ, Hunt SA, Alderman EL, Liang D, Yeung AC, Schroeder JS. Relation of donor age and preexisting coronary artery disease on angiography and intracoronary ultrasound to later development of accelerated allograft coronary artery disease. *J Am Coll Cardiol*. 1997;29:623-629.
42. Botas J, Pinto FJ, Chenzbraun A, et al. Influence of preexistent donor coronary artery disease on the progression of transplant vasculopathy. An intravascular ultrasound study. *Circulation*. 1995;92:1126-1132.
43. Tsutsui H, Ziada KM, Schoenhagen P, et al. Lumen loss in transplant coronary artery disease is a biphasic process involving early intimal thickening and late constrictive remodeling: results from a 5-year serial intravascular ultrasound study. *Circulation*. 2001;104:653-657.
44. Mehra MR, Ventura HO, Stapleton DD, Smart FW, Collins TC, Ramee SR. Presence of severe intimal thickening by intravascular ultrasonography predicts cardiac events in cardiac allograft vasculopathy. *J Heart Lung Transplant*. 1995;14:632-639.
45. Rickenbacher PR, Pinto FJ, Lewis NP, et al. Prognostic importance of intimal thickness as measured by intracoronary ultrasound after cardiac transplantation. *Circulation*. 1995;92:3445-3452.
46. Tuzcu EM, Kapadia SR, Sachar R, et al. Intravascular ultrasound evidence of angiographically silent progression in coronary atherosclerosis predicts long-term morbidity and mortality after cardiac transplantation. *J Am Coll Cardiol*. 2005;45:1538-1542.
47. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med*. 1995;333:621-627.
48. Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med*. 2003;349:847-858.
- 48b Koo BK, Hu X, Kang J et al. Fractional Flow Reserve or Intravascular Ultrasonography to Guide PCI. *N Engl J Med*. 2022; 387:779-789
49. Leesar MA, Saif I, Hagood KL, et al. A new method to optimize stent deployment by high-definition intravascular ultrasound. *J Invasive Cardiol*. 2021;33:E532-E539.
50. Prati F, Di Mario C, Moussa I, et al. In-stent neointimal proliferation correlates with the amount of residual plaque burden outside the stent: an intravascular ultrasound study. *Circulation*. 1999;99:1011-1014.
51. Zhang M, Matsumura M, Usui E, et al. Intravascular ultrasound-derived calcium score to predict stent expansion in severely calcified lesions. *Circ Cardiovasc Interv*. 2021;14(10):e010296.
52. Nakamura S, Colombo A, Gaglione A, et al. Intracoronary ultrasound observations during stent implantation. *Circulation*. 1994;89:2026-2034.
53. Kiemeneij F, Laarman G, Slagboom T. Mode of deployment of coronary Palmaz-Schatz stents after implantation with the stent delivery system: an intravascular ultrasound study. *Am Heart J*. 1995;129:638-644.

54. Colombo A, Hall P, Nakamura S, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation*. 1995;91:1676-1688.
55. Kasaoka S, Tobis JM, Akiyama T, et al. Angiographic and intravascular ultrasound predictors of in-stent restenosis. *J Am Coll Cardiol*. 1998;32:1630-1635.
56. de Jaegere P, Mudra H, Figulla H, et al. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC Study). *Eur Heart J*. 1998;19:1214-1223.
57. Hoffmann R, Mintz GS, Mehran R, et al. Intravascular ultrasound predictors of angiographic restenosis in lesions treated with Palmaz-Schatz stents. *J Am Coll Cardiol*. 1998;31:43-49.
58. Moussa I, Moses J, Di Mario C, et al. Does the specific intravascular ultrasound criterion used to optimize stent expansion have an impact on the probability of stent restenosis? *Am J Cardiol*. 1999;83:1012-1027.
59. Ziada KM, Kapadia SR, Belli G, et al. Prognostic value of absolute versus relative measures of the procedural result after successful coronary stenting: importance of vessel size in predicting long-term freedom from target vessel revascularization. *Am Heart J*. 2001;141:823-831.
60. de Feyter PJ, Kay P, Disco C, et al. Reference chart derived from post-stent implantation intravascular ultrasound predictors of 6 month expected restenosis on quantitative coronary angiography. *Circulation*. 1999;100:1777-1783.
61. Albiero R, Rau T, Schluter M, et al. Comparison of immediate and intermediate-term results of intravascular ultrasound versus angiography-guided Palmaz-Schatz stent implantation in matched lesions. *Circulation*. 1997;96:2997-3005.
62. Blasini R, Neumann FJ, Schmitt C, Walter H, Schomig A. Restenosis rate after intravascular ultrasound-guided coronary stent implantation. *Cathet Cardiovasc Diagn*. 1998;44:380-386.
63. Fitzgerald PJ, Oshima A, Hayase M, et al. Final results of the Can Routine Ultrasound Influence Stent Expansion (CRUISE) study. *Circulation*. 2000;102:523-530.
64. Choi JW, Goodreau LM, Davidson CJ. Resource utilization and clinical outcomes of coronary stenting: a comparison of intravascular ultrasound and angiographic guided stent implantation. *Am Heart J*. 2001;142:112-118.
65. Orford JL, Denktas AE, Williams BA, et al. Routine intravascular ultrasound scanning guidance of coronary stenting is not associated with improved clinical outcomes. *Am Heart J*. 2004;148:501-506.
66. Schiele F, Meneveau N, Vuilleminot A, et al. Impact of intravascular ultrasound guidance in stent deployment on 6-month restenosis rate: a multicenter, randomized study comparing two strategies—with and without intravascular ultrasound guidance. RESIST Study Group. REStenosis after IVUS guided Stenting. *J Am Coll Cardiol*. 1998;32:320-328.
67. Mudra H, di Mario C, de Jaegere P, et al. Randomized comparison of coronary stent implantation under ultrasound or angiographic guidance to reduce stent restenosis (OPTICUS study). *Circulation*. 2001;104:1343-1349.
68. Oemrawsingh PV, Mintz GS, Schali MJ, Zwinderman AH, Jukema JW, van der Wall EE. Intravascular ultrasound guidance improves angiographic and clinical outcome of stent implantation for long coronary artery stenoses: final results of a randomized comparison with angiographic guidance (TULIP Study). *Circulation*. 2003;107:62-67.
69. Sonoda S, Morino Y, Ako J, et al. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the SIRIUS trial. *J Am Coll Cardiol*. 2004;43:1959-1963.
70. Hong MK, Mintz GS, Lee CW, et al. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. *Eur Heart J*. 2006;27:1305-1310.
71. Doi H, Maehara A, Mintz GS, et al. Impact of post-intervention minimal stent area on 9-month follow-up patency of paclitaxel-eluting stents: an integrated intravascular ultrasound analysis from the TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent Trials. *JACC Cardiovasc Interv*. 2009;2(12):1269-1275.
72. Park SJ, Kim YH, Park DW, et al. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv*. 2009;2:167-177.
73. Andell P, Karlsson S, Mohammad MA, et al. Intravascular ultrasound guidance is associated with better outcome in patients undergoing unprotected left main coronary artery stenting compared with angiography guidance alone. *Circ Cardiovasc Interv*. 2017;10:e004813.
74. Witenbichler B, Maehara A, Weisz G, et al. Use of IVUS reduces stent thrombosis: results from the prospective, multicenter ADAPT-DES study. *Circulation*. 2014;129:463-470.
75. Degertekin M, Serruys PW, Tanabe K, et al. Long-term follow-up of incomplete stent apposition in patients who received sirolimus-eluting stent for de novo coronary lesions: an intravascular ultrasound analysis. *Circulation*. 2003;108:2747-2750.
76. Kume T, Waseda K, Ako J, et al. Intravascular ultrasound assessment of postprocedural incomplete stent apposition. *J Invasive Cardiol*. 2012;24(1):13-16.
77. Cook S, Wenaweser P, Togni M, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation*. 2007;115:2426-2434.
78. Fujii K, Carlier SG, Mintz GS, et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol*. 2005;45(7):995-998.
79. Hong MK, Mintz GS, Lee CW, et al. Incidence, mechanism, predictors, and long-term prognosis of late stent malapposition after bare-metal stent implantation. *Circulation*. 2004;109:881-886.
80. Hong MK, Mintz GS, Lee CW, et al. Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. *Circulation*. 2006;113:414-419.
81. Hong SJ, Kim BK, Shin DH, et al. Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JAMA*. 2015;314(20):2155-2163.
82. Zhang J, Gao X, Kan J, et al. Intravascular Ultrasound versus angiography-guided drug-eluting stent implantation: the ULTIMATE trial. *J Am Coll Cardiol*. 2018;72:3138-3141.
83. Hong SJ, Mintz GS, Ahn CM, et al. Effect of intravascular ultrasound-guided drug-eluting stent implantation: 5-year follow-up of the IVUS-XPL randomized trial. *J Am Coll Cardiol Interv*. 2020;13(1):62-71.
84. Gao XF, Ge Z, Kong XQ, et al. 3-year outcomes of the ULTIMATE trial comparing intravascular ultrasound versus angiography-guided drug-eluting stent implantation. *J Am Coll Cardiol Interv*. 2021;14(3):247-257.
85. Elgendy IY, Mahmoud AN, Elgendy AY, Mintz GS. Intravascular ultrasound guidance is associated with lower cardiovascular mortality and myocardial infarction for drug-eluting stent implantation—insights from an updated meta-analysis of randomized trials. *Circ J*. 2019;83:1410-1413.
86. Hong SJ, Zhang JJ, Mintz GS, et al. Improved 3-year cardiac survival after intravascular ultrasound-guided long drug-eluting stent implantation: a patient-level analysis from 2 randomized trials. *J Am Coll Cardiol Interv*. 2021;15:208-216.
- 86b. Lee JM, Choi KH, Song YB et al. Intravascular Imaging-Guided or Angiography-Guided Complex PCI. *N Engl J Med* 2023, March 5, DOI: 10.1056/NEJMoa2216607
87. Painter JA, Mintz GS, Wong SC, et al. Serial intravascular ultrasound studies fail to show evidence of chronic Palmaz-Schatz stent recoil. *Am J Cardiol*. 1995;75:398-400.
88. Hoffmann R, Mintz GS, Dussallant GR, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. *Circulation*. 1996;94:1247-1254.
89. Lemos PA, Saia F, Ligthart JM, et al. Coronary restenosis after sirolimus-eluting stent implantation: morphological description and mechanistic analysis from a consecutive series of cases. *Circulation*. 2003;108:257-260.
90. Castagna MT, Mintz GS, Leiboff BO, et al. The contribution of “mechanical” problems to in-stent restenosis: an intravascular ultrasonographic analysis of 1090 consecutive in-stent restenosis lesions. *Am Heart J*. 2001;142:970-974.
91. Sharma SK, Kini A, Mehran R, Lansky A, Kobayashi Y, Marmur JD. Randomized trial of Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-stent Restenosis (ROSTER). *Am Heart J*. 2004;147:16-22.
92. vom Dahl J, Dietz U, Haager PK, et al. Rotational atherectomy does not reduce recurrent in-stent restenosis: results of the angioplasty versus rotational atherectomy for treatment of diffuse in-stent restenosis trial (ARTIST). *Circulation*. 2002;105:583-588.
93. Waiha W, Bil J, Januszek R, et al. Long-term outcomes of drug-eluting balloons versus thin-strut drug-eluting stents for treatment of in-stent restenosis (DEB-Dragon-Registry). *Circ Cardiovasc Interv*. 2021;14(9):e010868.
94. Shlofmitz E, Matsumura M, Maehara A, et al. Impact of shockwave intravascular lithotripsy induced calcium fracture for treatment of stent underexpansion mediated in-stent restenosis. *J Am Coll Cardiol*. 2021;8(19 suppl S): B111-B112.
95. Maehara A, Mintz GS, Bui AB, et al. Incidence, morphology, angiographic findings, and outcomes of intramural hematomas after percutaneous coronary interventions: an intravascular ultrasound study. *Circulation*. 2002;105:2037-2042.
96. Schühlen H, Hadamitzky M, Walter H, Ulm K, Schomig A. Major benefit from antiplatelet therapy for patients at high risk for adverse cardiac events after coronary Palmaz-Schatz stent placement: analysis of a prospective risk stratification protocol in the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial. *Circulation*. 1997;95:2015-2021.
97. Ziada KM, Tuzcu EM, De Franco AC, et al. Intravascular ultrasound assessment of the prevalence and causes of angiographic “haziness” following high-pressure coronary stenting. *Am J Cardiol*. 1997;80:116-121.
98. Park Y, Park HS, Jang GL, et al. Intravascular ultrasound guided recanalization of stumple chronic total occlusion. *Int J Cardiol*. 2011;148(2):174-178.
99. Okamura A, Iwakura K, Date M, et al. Navifocus WR is the promising intravascular ultrasound for navigating the guidewire into true lumen during the coronary intervention for chronic total occlusion. *Cardiovasc Interv Ther*. 2014;29(2):181-186.
100. Rathore S, Katoh O, Tuschikane E, Oida A, Suzuki T, Takase S. A novel modification of the retrograde approach for the recanalization of chronic total occlusion of the coronary arteries intravascular ultrasound-guided reverse controlled antegrade and retrograde tracking. *JACC Cardiovasc Interv*. 2010;3(2):155-164.
101. Losordo DW, Rosenfield K, Kaufman J, Pieczek A, Isner JM. Focal compensatory enlargement of human arteries in response to progressive atherosclerosis. In vivo documentation using intravascular ultrasound. *Circulation*. 1994;89:2570-2577.
102. Pasterkamp G, Wensing PJ, Post MJ, et al. Paradoxical arterial wall shrinkage may contribute to luminal narrowing in human atherosclerotic femoral arteries. *Circulation*. 1995;91:1444-1449.



103. Arthurs ZM, Bishop PD, Feiten LE, et al. Evaluation of peripheral atherosclerosis: a comparative analysis of angiography and intravascular ultrasound imaging. *J Vasc Surg*. 2010;51:933-938.
104. Toggweiler S, Leipsic J, Binder RK, et al. Management of vascular access in transcatheter aortic valve replacement: part 1: basic anatomy, imaging, sheaths, wires, and access routes. *JACC Cardiovasc Interv*. 2013;6(7):643-653.
105. Walker TG, Kalva SP, Yeddula K, MBBS, et al. Clinical Practice Guidelines for Endovascular Abdominal Aortic Aneurysm Repair: Written by the Standards of Practice Committee for the Society of Interventional Radiology and Endorsed by the Cardiovascular and Interventional Radiological Society of Europe and the Canadian Interventional Radiology Association. *J Vasc Interv Radiol*. 2010;21:1632-1655.
106. Saket RR, Razavi MK, Padidar A, et al. Novel intravascular ultrasound-guided method to create transintimal arterial communications: initial experience in peripheral occlusive disease and aortic dissection. *J Endovasc Ther*. 2004;11(3):274-280.
107. Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. *Circulation*. 2000;101:598-603.
108. Mintz GS, Garcia-Garcia HM, Nicholls SJ, et al. Clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound regression/progression studies. *EuroIntervention*. 2011;6(9):1123-1130.
109. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291:1071-1080.
110. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA*. 2006;295(13):1556-1565.
111. Nicholls SJ, Hsu A, Wolski K, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol*. 2010;55(21):2399-2407.
112. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. *Circulation*. 2002;106:2200-2206.
113. Rodriguez-Granillo GA, Garcia-Garcia HM, Mc Fadden EP, et al. In vivo intravascular ultrasound-derived thin-cap fibroatheroma detection using ultrasound radiofrequency data analysis. *J Am Coll Cardiol*. 2005;46:2038-2042.
114. Sales FJ1, Falcão BA, Falcão JL, et al. Evaluation of plaque composition by intravascular ultrasound "virtual histology": the impact of dense calcium on the measurement of necrotic tissue. *EuroIntervention*. 2010;6(3):394-399.
115. Pu J, Mintz GS, Brilakis ES, et al. In vivo characterization of coronary plaques: novel findings from comparing greyscale and virtual histology intravascular ultrasound and near-infrared spectroscopy. *Eur Heart J*. 2012;33(3):372-383.
116. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364:226-235.
117. Gardner CM, Tan H, Hull EL, et al. Detection of lipid core coronary plaques in autopsy specimens with a novel catheter-based near-infrared spectroscopy system. *J Am Coll Cardiol Img*. 2008;1:638-648.
118. Maddur RD, Steinberg DH, Anderson RD. Multimodality direct coronary imaging with combined near-infrared spectroscopy and intravascular ultrasound: initial US experience. *Catheter Cardiovasc Interv*. 2013;81:551-557.
119. Waksman R, Mario CD, Torguson R, et al. Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: a prospective, cohort study. *Lancet*. 2019;394:1629-1637.
120. Waters KR, Bautista R, Zelenka R, et al. Development of a high-definition intravascular ultrasound imaging system and catheter. *IEEE Int Ultrason Symp Proceedings*. 2011:1762-1765.
121. García-Guimaraes M, Cuesta J, Rivero F, Bastante T, Benedicto A, Alfonso F. High-definition intravascular ultrasound vs optical coherence tomography: preliminary experience. *Rev Esp Cardiol*. 2018;71:119-120.
122. Ono M, Kawashima H, Hara H, et al. Advances in IVUS/OCT and future clinical perspective of novel hybrid catheter system in coronary imaging. *Front Cardiovasc Med*. 2020;7:119.
123. Waksman R, Kitabata H, Prati F, Albertucci M, Mintz GS. Intravascular ultrasound versus optical coherence tomography guidance. *J Am Coll Cardiol*. 2013;62(suppl):S32-S40.
124. Maehara A, Mintz GS, Stone GW. OCT versus IVUS: accuracy versus clinical utility. *J Am Coll Cardiol Img*. 2013;6:1105-1107.



17

Optical Coherence Tomography

TOM ADRIAENSSENS, JAMES FUJIMOTO AND IK-KYUNG JANG

INTRODUCTION, 319

PHYSICS OF OPTICAL COHERENCE TOMOGRAPHY, 319

IMAGE ACQUISITION BY FREQUENCY DOMAIN OPTICAL COHERENCE TOMOGRAPHY, 320

Frequency Domain Optical Coherence Tomography, 320

Potential Risks and Complications, 321

Angio Optical Coherence Tomography Co-registration, 321

Automated Measurements, 321

EVALUATION OF CORONARY PATHOLOGY, 321

Normal Artery, 321

Lipid Plaque, 322

Fibrous and Fibrocalcific Plaque, 322

Intraluminal and Intramural Pathology Seen by Optical Coherence Tomography, 322

Thin-Cap Fibroatheroma, 323

PITFALLS OF IMAGE INTERPRETATION, 325

ASSESSMENT OF CORONARY PLAQUE CHARACTERISTICS, 326

Plaque Destabilization and Progression: The Layered Plaque, 326

Intraplaque Hemorrhage, 326

Effect of Intensive Statin Therapy, 326

Etiology of the Acute Coronary Syndromes, 326

Ruptured Thin-Cap Fibroatheroma, 326

Plaque Erosion, 326

The Calcified Culprit Plaque, 327

The Nonculprit Coronary Plaque in Acute Coronary Syndromes, 328

Myocardial Infarction with Nonobstructive Coronary Atherosclerosis, 328

ROLE OF OPTICAL COHERENCE TOMOGRAPHY IN PERCUTANEOUS CORONARY INTERVENTION, 328

Before Stent Deployment, 328

Bifurcation Intervention, 329

Immediate Poststent Deployment, 329

Stent Expansion, 330

Malapposition, 331

Edge Dissection, 331

Tissue Protrusion, 332

Late Stent Evaluation, 332

Neoatherosclerosis, 332

Stent Thrombosis, 333

In-Stent Restenosis, 333

Transplant Vasculopathy, 334

FUTURE DIRECTIONS, 334

Combined Morphologic and Functional Assessment, 334

Multimodality Systems, 334

Micro-optical Optical Coherence Tomography, 334

CONCLUSION, 334

SUMMARY, 334

INTRODUCTION

Optical coherence tomography (OCT) is a tomographic imaging technology that allows real-time ultra-detailed intravascular imaging. The resolution of OCT is significantly higher than for other currently available intravascular imaging modalities, allowing for detailed characterization of the morphologic features of coronary arteries, coronary plaques, and intracoronary stents. OCT is analogous to intravascular ultrasonography (IVUS) with light as the energy source instead of sound.^{1,3} Light is directed at a target, and the magnitude and echo time delay of the back-scattered light signal is measured. Because it uses light, OCT has a resolution that is an order of magnitude greater than IVUS. Because of significant blood attenuation of light, OCT imaging requires a blood-free zone for imaging. First-generation OCT imaging systems (time-domain OCT) used an occlusive balloon with saline flush through a distal balloon lumen. Second-generation OCT systems (frequency or Fourier-domain OCT), using a nonocclusive contrast flushing method to create a blood-free zone combined with faster catheter pullback, have significantly simplified image acquisition. These improvements have allowed for a rapid expansion of OCT use. In the clinical research field, this has led to important insights into the pathobiology of the coronary plaque, mechanisms underlying plaque progression, the healing characteristics of the vessel wall after stent implantation, and the failure mechanisms of drug-eluting stents (DESs) and bioresorbable vascular scaffolds, among

others. In daily practice in the catheterization laboratory, OCT is used for elucidation of cases with unclear angiographic findings, the assessment of stent failure and guidance of complex coronary intervention procedures. The results of several key large randomized clinical trials (ILUMIEN IV [Optical Coherence Tomography (OCT) Guided Coronary Stent IMplantation Compared to Angiography: a Multicenter Randomized Trial in PCI], OCTOBER [European Trial on Optical Coherence Tomography Optimized Bifurcation Event Reduction-The OCTOBER Trial]) will hopefully shed further light on the role of OCT in percutaneous coronary intervention (PCI) optimization.

PHYSICS OF OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography uses optical interference of near-infrared light to generate images.^{1,3} Near-infrared light is emitted from the distal tip of an optical fiber located within the imaging catheter and directed at the target tissue (Figure 17.1). When light encounters a boundary between objects with varying optical impedances, a portion of the light is backscattered. The OCT catheter measures the magnitude and echo time delay of the backscattered light signal. To allow for recording of the reflected light, an interferometer is used to combine the reflected light from the sample with a reference beam reflected off a reference mirror at a known distance. The differences in signals from

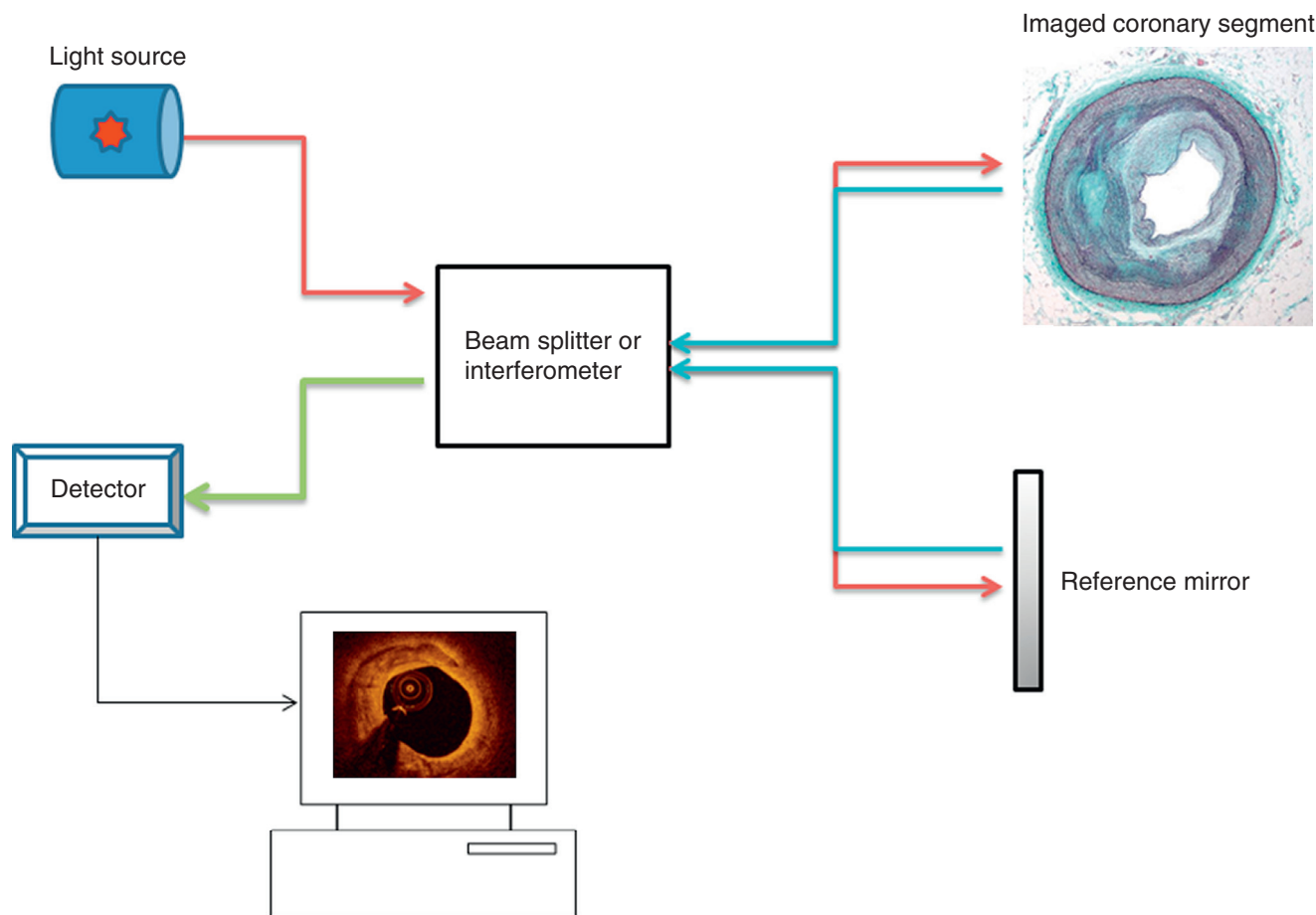


FIGURE 17.1 Near-infrared light is directed at a target and a reference mirror. Interference occurs when light from the sample and reference mirror arrive at the same time. The magnitude and echo time delay of the reflected light signal are measured. To allow for recording of the reflected light, an interferometer is used to combine the reflected light from the sample with a reference beam reflected off a reference mirror at a known distance. The summed beams from the sample and the reference mirror are then measured by the detector. In a time domain (TD) optical coherence tomography (OCT) system, the reference mirror moves back and forth, allowing for measurement of depth. In a Fourier domain (FD) OCT system, the light sources sweep across a frequency range. Because mechanical sweep of the reference mirror is not necessary, image acquisition is significantly faster with FD-OCT. (From Abtahian F, Jang IK. Optical coherence tomography: basics, current application and future potential. *Curr Opin Pharmacol*. 2012;12:583-591.)

the sample and from the reference mirror are then measured by the interferometer. The first-generation time domain OCT (TD-OCT) systems used a broadband light source and determined tissue depth by differences in the distance to the reference mirror.⁴ Because of the need for mechanical sweep of the reference light source, the rate of image acquisition in TD-OCT is inherently limited. Maximum pull-back speeds with TD-OCT systems are approximately 2 to 3 mm/s. In the context of the need for a blood-free field, this limits the length of coronary artery that can be imaged during one pullback of the imaging catheter. In second-generation frequency (or Fourier)-domain OCT (FD-OCT) systems, the light source is monochromatic and emits various wavelengths between 1250 and 1350 nm in a continuous sweep.⁵ Fourier transformation of the interference signal generated allows for calculation of the reflections returning from different depths. As a result, there is no need for mechanical adjustment of the reference light path. This allows all echo time delays to be measured simultaneously, leading to significantly faster image acquisition. FD-OCT systems allow pullback speeds of the imaging catheter up to 40 mm/s.

Because light is the energy source, tissue can be imaged with an axial resolution of 10 μm and lateral resolution of

20 μm .⁶ Tissue penetration is limited to a depth of 2 mm but varies significantly depending on the tissue imaged. Lipid, which is highly attenuating, allows for significantly less tissue penetration than collagen or calcium, which are low attenuating. In comparison, IVUS provides a resolution of 150 to 250 μm to a depth of up to 10 mm.⁷

IMAGE ACQUISITION BY FREQUENCY DOMAIN OPTICAL COHERENCE TOMOGRAPHY

Frequency Domain Optical Coherence Tomography

Currently, the most commonly available commercial OCT system in the United States and Europe is the ILUMIEN Optis, a FD-OCT system manufactured by Abbott Vascular (https://www.accessdata.fda.gov/cdrh_docs/pdf18/K183320.pdf). In this second-generation platform, the optical probe is integrated into a delivery catheter with a profile of 2.7 Fr and a length of 140 cm. The catheter has a rapid exchange monorail tail compatible with standard 0.014-inch coronary wires and can be delivered via a 6-Fr guide catheter. The Dragonfly Optis catheter (Abbott Vascular)

(<https://www.accessdata.fda.gov/CDRH510K/K141453.pdf>) has three radiopaque markers, the first identifying the distal tip, the second the location of the imaging lens (27 mm from the tip), and the third 50 mm proximal to the lens. These allow for alignment of the catheter with the vessel segment of interest. A newer version, the Dragonfly Opstar (Abbott Vascular) (<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K192019>), has a redesigned shaft and a lower crossing profile. The distance of the lens to the tip of the catheter is shorter (23 mm), to accommodate for distal lesion imaging, and the most proximal marker is at 75 mm, indicating the end of a standard 75-mm pullback. During the pullback of the imaging catheter, the optic fiber probe is pulled along the catheter sheath. The system contains a dedicated pullback device and a console that processes and stores the data. The ILUMIEN OPTIS imaging system allows for imaging of a 75-mm vessel segment at a pullback speed of 36 mm/s. Because of the rapid pullback in these systems, adequate blood displacement can be achieved with a single bolus injection of contrast. The guiding catheter should be positioned coaxially with the vessel ostium to maximize delivery of contrast for blood clearance. The manufacture protocol recommends a 14- to 16-mL injection of contrast at a rate of 4 mL/s at 400 PSI in the left coronary artery and 3 mL/s at 300 PSI in the right coronary artery. Administration of the contrast medium can be done by hand injection or by use of an automated injector pump. The system allows for real-time three-dimensional (3D) reconstruction of the imaged vessel. Although the 3D reconstruction of images usually does not offer important additional value with respect to image interpretation, it can play an adjunctive role in certain specific situations, such as bifurcation intervention.

Other commercially available systems include the Lunawave coronary Optical Frequency Domain Imaging (OFDI) system, used in conjunction with the FastView coronary catheter (Terumo Corporation), and the most recently Food and Drug Administration–approved Gentuity HF-OCT Imaging System with Vis-Rx Micro-Imaging Catheter (https://www.accessdata.fda.gov/cdrh_docs/pdf19/K192922.pdf). The latter system, named high-frequency (HF)-OCT, is characterized by faster acquisition and pullback speeds and a larger field of view, enabling its use in coronary as well as cerebral vasculature.⁸

Potential Risks and Complications

The use of intracoronary imaging implies, by definition, the manipulation of devices in the coronary artery. In line with the rules applying for any coronary intervention, skilled training and dedicated care with respect to manipulation of the guiding catheter and the imaging catheter are mandatory for safe application of this technology in patient care. Coronary spasm and coronary dissection are potential complications whenever any device is introduced into a coronary artery and likewise can occur during OCT imaging. To reduce the risk of coronary spasm, intracoronary nitroglycerin should be administered before image acquisition. Anticoagulation before intracoronary introduction of the OCT system is mandatory.

In a contemporary report, Van der Sijde et al.⁹ described complications related to the OCT imaging procedure in

0.6% of patients (a number comparable to cases using IVUS). All events were self-limiting after retrieval of the imaging catheter or easily treatable in the catheterization laboratory. As discussed earlier, the implementation of FD-OCT obviates the need for vessel occlusion and implies much shorter periods of vessel flushing compared with the earlier TD-OCT imaging systems. This has resulted in a substantial decrease in ischemia-related symptoms and the risk for arrhythmias during image acquisition.^{10,11}

Angio Optical Coherence Tomography Co-registration

The potential benefits of real-time co-registration of OCT images with angiography, allowing for exact localization of the acquired OCT frame on the corresponding angiogram, has fostered the development of integrated co-registration systems.¹² In the Impact of Real-time Angiographic Co-registered OCT on PCI Results - the Randomized OPTICO-integration II Study (OPTICO-integration study), real-time OCT angiography co-registration had a favorable impact on PCI outcome, reducing the composite endpoint of major edge dissection and longitudinal geographical miss.¹³ However, a clear impact on hard clinical endpoints will remain hard to prove.

Automated Measurements

With a huge number of cross-sectional images provided in each single OCT acquisition and the need for accurate and reproducible interpretation in the setting of an invasive procedure, there is a need for automated measurement tools to assist the OCT operator. When adequate image quality is achieved, the sharp demarcation of the lumen borders allows for a reliable automated assessment of lumen borders, lumen area, and percentage area stenosis. These automated measurements have been implemented in the manufacturer's software, and given its superior resolution, the reproducibility for these measures is better for OCT than for IVUS.¹⁴ The automated detection of stent struts adds an important level of complexity. Ughi et al.¹⁵ reported a method for automated analysis that reliably detects metallic intracoronary stent struts on OCT, allowing for measurements of the distance between the strut and the lumen border. This software application was the first enabling automated assessment of stent strut coverage and apposition in OCT images.

More recently, automated measurement applications based on artificial intelligence (AI) solutions have been proposed. AI broadly refers to analytical algorithms that iteratively learn from data, allowing computers to find hidden insights without being explicitly programmed where to look.¹⁶ Deep learning models for plaque characterization, detection of thin-cap fibroatheroma (TCFA), and assessment of stent strut coverage and apposition have been proposed.¹⁷⁻²⁰

EVALUATION OF CORONARY PATHOLOGY

Normal Artery

On histology, the normal coronary artery has three tissue layers: intima, media, and adventitia separated by an internal

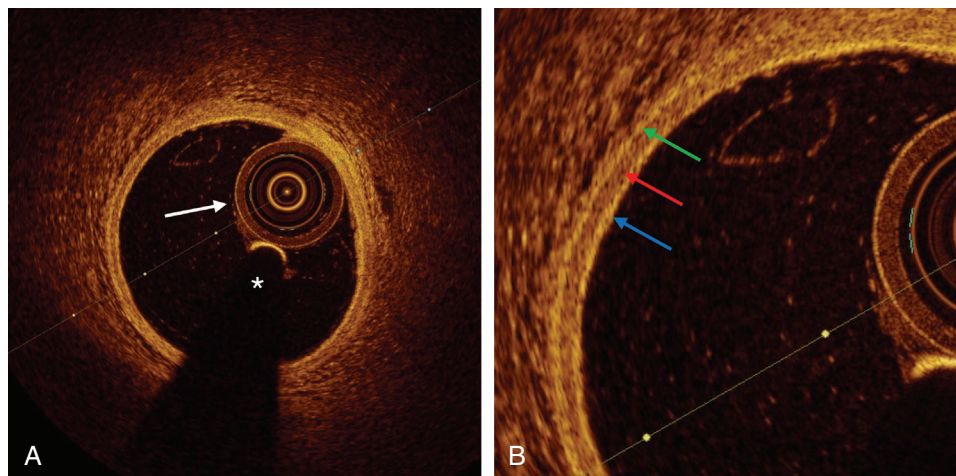


FIGURE 17.2 Optical coherence tomography (OCT) images from a normal coronary artery (A) with magnification (B). OCT catheter (white arrow) within a coronary artery reveals the normal three layers of the coronary artery: the intima (blue arrow), media (red arrow), and adventitia (green arrow). The guidewire causes a shadow artifact (asterisk).

and external elastic lamina (EEL). All three layers can be visualized by OCT in a normal artery (Figure 17.2). The innermost adluminal intimal layer is seen by OCT as a signal-rich thin band.²¹⁻²³ The media is immediately behind the intima and appears as an area of low signal intensity surrounded by the signal-rich adventitia. OCT assessment of intimal thickness is highly accurate,²² allowing for detection of the earliest marker of atherosclerotic disease, intimal thickening.²⁴ Coronary plaques are typically identified by the presence of focal thickening and loss of the normal three-layered structure of the coronary artery. Mature coronary plaques are generally classified by histology as lipid rich, fibrous, or fibrocalcific based on their tissue compositions,²⁵ each of which can be distinguished by its OCT appearance. In cadaveric studies of human arteries with histology as the gold standard, OCT had sensitivities of 95%, 98%, and 100% for lipid plaque, fibrous plaque, and calcified plaque, respectively. The specificity of OCT for the same three plaque tissue components was 98%, 94%, and 100%, respectively.²⁶

Lipid Plaque

Lipid plaque is defined by the presence of signal-poor areas with diffuse borders resulting from backscatter and rapid attenuation from the lipid-containing region located below a fibrous cap (Figure 17.3A). The fibrous cap is typically a homogeneous signal-rich band overlying the signal-poor lipid core. The minimal thickness of the fibrous cap is critical for identifying TCFAs.²⁷

Fibrous and Fibrocalcific Plaque

Fibrous plaques are visualized on OCT as homogeneous areas with high reflectivity and low attenuation (Figure 17.3B). Calcification within the coronary artery is demarcated by a signal-poor region with sharp edges and low attenuation (Figure 17.3C).²⁸ This is distinct from lipid pools that are signal-poor areas with diffuse borders and high attenuation. Because both calcium and lipid generate low

backscatter, distinguishing calcified plaque from lipid-rich plaque can at times be difficult to untrained interpreters.²⁹

Intraluminal and Intramural Pathology Seen by Optical Coherence Tomography

Macrophages

Increased inflammation and macrophage infiltration are hallmarks of vulnerable plaques. Macrophages appear on OCT as bright spots with a high signal attenuation behind them^{21,30,31} (Figure 17.3D). The link between plaque instability and the presence of macrophages is established, with reports of greater macrophage density in patients with ST-elevation myocardial infarction (STEMI) compared with those with stable angina,³² in culprit compared with nonculprit plaques,³³ and in TCFA compared with non-TCFA lesions.³⁴

Cholesterol Crystals

Cholesterol crystals are identified by the presence of linear signal streaks, typically in the context of a lipid-rich plaque (Figure 17.3E). The accuracy of OCT for the detection of cholesterol crystals has not been fully validated by histology. In a comparative study between OCT images and histopathology sections, a high specificity but only modest sensitivity was found.³⁵

Microchannels

Optical coherence tomography can detect microchannels within coronary plaque that appear as tubuloluminal structures with no signal inside (Figure 17.3F). These are believed to represent neovascularization and are found in higher abundance in thin-capped lipid plaques and in patients presenting with plaque rupture. The presence of microchannels has also been associated with plaque progression.³⁶

Thrombus

Thrombus is identified by the presence of an irregular mass either attached to the vessel wall (mural thrombus)

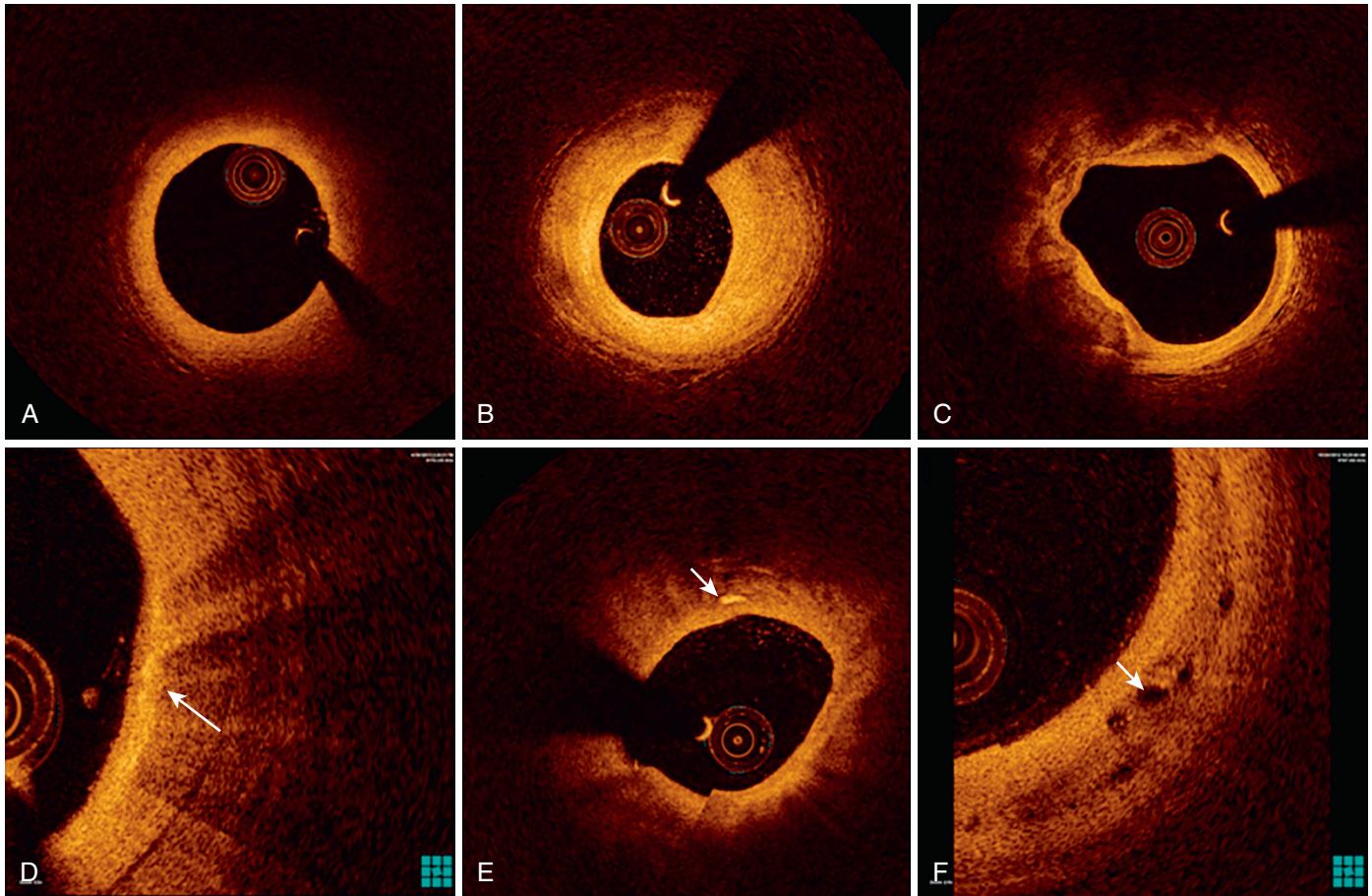


FIGURE 17.3 Optical coherence tomography images of coronary pathology. **A**, Circumferential lipid-rich plaque. **B**, Fibrous plaque. **C**, Fibrocalcific plaque. **D**, Macrophages (arrow). **E**, Cholesterol crystal (arrow). **F**, Microchannels (arrow).

or free floating within the vessel lumen. Platelet-rich white thrombus is a homogeneous signal-rich mass with low attenuation resulting in minimal shadowing, whereas red thrombus is a mass with rapid attenuation resulting in significant shadowing (Figure 17.4A and B).²⁸

Others

In addition to coronary plaques, acute coronary syndromes (ACSs) can be caused by spontaneous coronary artery dissection (SCAD) and vasospasm. The prevalence of SCAD is substantially higher in premenopausal women presenting with ACS.³⁷ OCT is sensitive for detecting and characterizing coronary dissections and may be useful in guiding interventions to treat the dissection (Figure 17.4C).^{38,39} The presence of double-lumen, dissection flap, or intramural hematoma can be readily visualized by OCT even when angiographically not obvious. However, in general, significant SCAD can be diagnosed angiographically, and any instrumentation of a dissected vessel inherently carries risks of dissection propagation and vessel closure. Therefore, most operators choose a conservative treatment approach when coronary flow is preserved or restored.⁴⁰

The morphologic changes, specifically medial contraction and intimal gathering, that underlay coronary vasospasm have also been visualized by OCT.² Thrombus with lumen irregularity was observed in one-fifth and lumen

irregularity without overlying thrombus in nearly two-thirds of patients.⁴¹ These findings contradict the common belief of a perfectly healthy vessel architecture at the site of coronary vasospasm and can be seen as an argument in favor of the administration of antiplatelet therapy in selected patients with this condition.

Thin-Cap Fibroatheroma

Coronary artery disease (CAD) is the leading cause of death worldwide, most often by precipitating ACS. ACS are acute manifestations of the chronic process of atherosclerosis. With respect to plaque rupture, there has been significant interest in understanding the mechanism by which CAD that is otherwise asymptomatic can lead to a sudden myocardial infarction (MI). The term “vulnerable plaque” was initially coined in reference to coronary stenosis that did not appear to be significant by angiography but subsequently caused acute MI.^{42,43} Vulnerable plaques can be present in any location within the coronary arteries but are most commonly found in the proximal portion of the three main coronary vessels often at or near bifurcations.^{36,44-46} When a vulnerable plaque ruptures, the thrombogenic contents of the plaque are exposed to blood. Vulnerable plaques that are at high risk of precipitating an acute coronary event appear to have several histologic

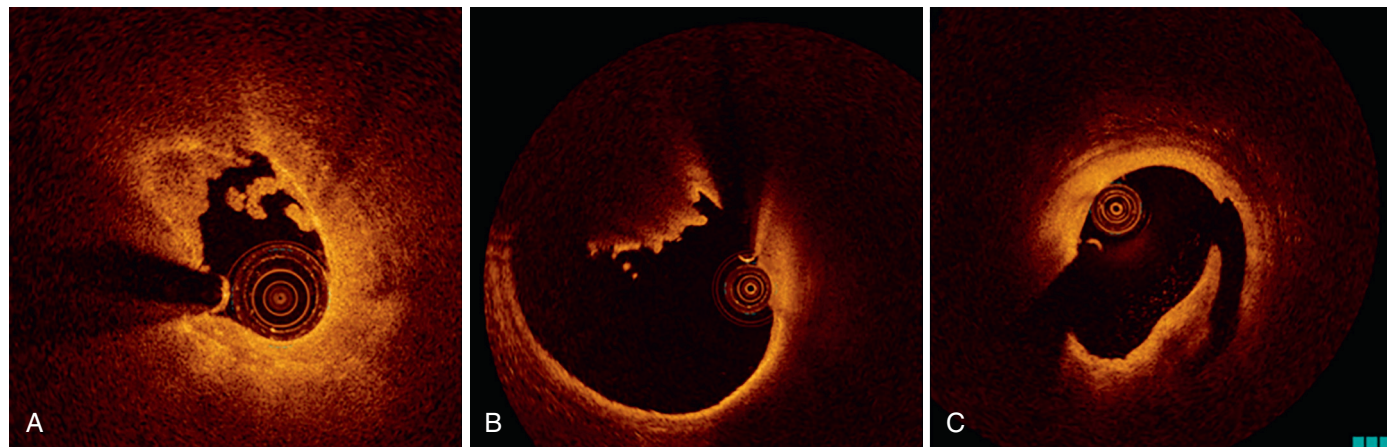


FIGURE 17.4 Optical coherence tomography (OCT) examples of intracoronary pathology. **A**, Platelet-rich white thrombus. **B**, Red blood cell-rich red thrombus. **C**, Dissection.

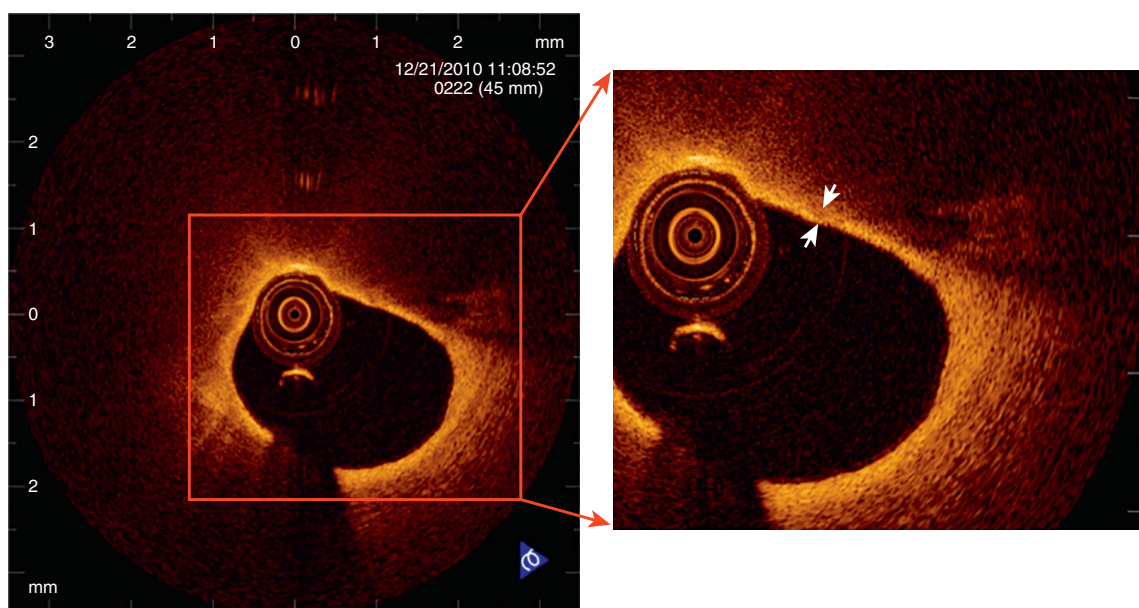


FIGURE 17.5 Example of thin-cap fibroatheroma (TCFA). The thinnest fibrous cap thickness (arrows) of a lipid-rich plaque is measured. Lipid-rich plaques with a minimal cap thickness of 65 μm or less are typically defined as TCFA.

features that distinguish them from more stable coronary plaques. Autopsy studies have identified the presence of thin fibrous caps ($<65 \mu\text{m}$), large lipid cores ($>40\%$ of the overall plaque volume), and increased infiltration of macrophages into the plaque cap as the most common features of high-risk coronary plaques⁴⁷ (Figure 17.5). In addition, several other features have been linked to vulnerable plaques, including positive remodeling of the affected vessel, increased vasa-vasorum neovascularization, and intraplaque hemorrhage. Because of a resolution capability of 10 μm , OCT is the only modality that can readily identify and measure the thin fibrous caps of vulnerable plaques. Many studies have used 65 μm as cutoff for TCFA based on postmortem histology studies.^{48,49} This has been adopted as well in the summary of the international working group of standardization of OCT.²¹ However, it must be acknowledged that many methodologic issues remain with respect to the exact and reproducible measurement of the thin cap, such as two-dimensional measurements of a 3D

structure, the presence of thrombus obscuring the thinnest part of the cap, and differences between the ruptured and nonruptured site of the plaque.

In a direct postmortem comparison of OCT and histology, Brown et al.⁵⁰ identified a fibrous cap thickness (FCT) of 85 μm or greater over three continuous frames to be the optimal definition for the identification of histopathologic TCFA. Potential discrepancies between OCT and postmortem histology might be explained by tissue shrinkage occurring during tissue preparation.²¹ In conclusion, the specific cutoff value for defining a TCFA has been the matter of debate that has not been settled thus far.

Apart from methodologic issues with measurement of cap thickness, recent studies have provided disappointing results with respect to the positive predictive value for OCT to discriminate TCFA.⁵⁰⁻⁵² Phipps et al.⁵³ reported foam cell infiltration at the cap site and shallow or tangential beam angulation as common causes for the discrepancy between OCT and histopathology of TCFA. These

limitations should be kept in mind when interpreting the results of studies reporting natural history or response to therapy of OCT-identified TCFA.

PITFALLS OF IMAGE INTERPRETATION

Recognition of potential artifacts and the limitations of OCT is crucial in proper interpretation of images and study results. Incomplete clearance of blood is one of the most common causes of artifact during OCT imaging. Residual blood attenuates the light beam, resulting in limited visualization of the vessel (Figure 17.6A). Significant blood attenuation can hamper accurate measurement of vessel size and can easily be confused for thrombus. Because of the limited tissue penetration of OCT to 2 to 3 mm, determining the composition of thick plaques can become problematic with increasing signal drop-off. Attenuation of OCT signal deep within the artery wall can be confused for lipid pool, and alternatively, deep lipid can be misinterpreted as signal attenuation. Similarly, lack of tissue penetration prevents accurate measurement of total plaque burden and precludes assessing for vessel remodeling.

Optical coherence tomography imaging artifacts include the following:

- Shadowing is a result of signal drop-off distal to an object such as guidewire (Figure 17.6B), stent strut

(Figure 17.6C), blood within the vessel or within the imaging catheter, macrophages, and thrombus. As a result of signal loss, the underlying vessel structure cannot be visualized.

- Tangential signal dropout occurs when a catheter is nearly adjacent to a vessel wall, resulting in light being directed almost parallel with the vessel surface. As a result, the light source is significantly attenuated, and there can be significant signal drop-off below the vessel lumen surface in the area immediately adjacent to the imaging catheter. It is important not to confuse this artifact with pathologic causes of signal-poor regions within vessel walls such as lipid-rich plaques.
- Nonuniform rotation distortion arises as a consequence of binding of the rotating optical components during image acquisition, typically caused by a defective catheter or during imaging of tortuous or calcified vasculature or through a narrow stenosis. It can also occur when the Y-connector of the catheter system is connected too tight around the imaging catheter, and by doing so, hampers a smooth movement of the imaging catheter components during image acquisition. It appears as a smearing of the OCT image in the circumferential direction.
- Saturation artifact (Figure 17.6D) is caused by objects with highly reflective surface causing such high back-scatter that they cannot be detected accurately. This results in linear streaks along an axial direction.

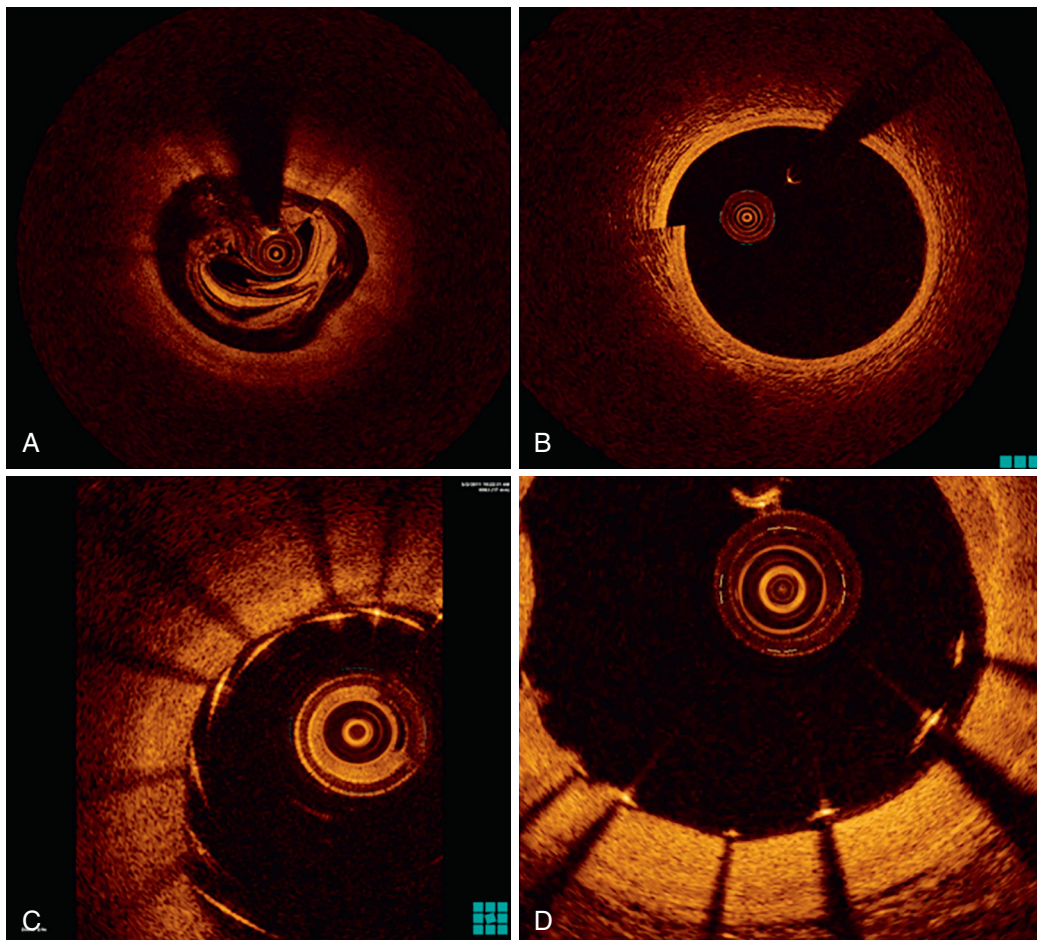


FIGURE 17.6 Examples of image artifacts. **A**, Blood artifact. **B**, Motion artifact. **C**, Merry-go-round and sunflower artifacts. **D**, Saturation artifact.

Saturation artifact is typically caused by stent struts and guidewires.

- Motion artifact is caused by movement of the artery with respect to the imaging catheter (see [Figure 17.6B](#)). It was a more significant problem with the older TD-OCT systems that had a slower pullback speed and therefore acquired images over significantly more cardiac cycles. Seam lines, which are axial discontinuities, can arise when the imaging catheter moves relative to the vessel lumen during the acquisition of a single cross section.
- Fold-over artifacts are specific to FD-OCT systems. They occur when the vessel lumen is larger than the imaging depth of the OCT system. They typically occur at the level of large bifurcations and appear as if the side walls of the artery are folded over into the lumen of the artery.
- Merry-go-round and sunflower effects are caused by eccentric wire positions that result in a light beam that is not perpendicular relative to the artery wall (see [Figure 17.6C](#)).⁵⁴ Lateral resolution in the wall distal to the position of the wire is reduced (“merry-go-round effect”), and the reflection of stent struts aligns toward the location of the wire, making it appear as if the stent struts are bending toward the wire (“sunflower effect”).

ASSESSMENT OF CORONARY PLAQUE CHARACTERISTICS

Plaque Destabilization and Progression: The Layered Plaque

In recent years, evidence has accrued that in many cases, the progression of atherosclerotic plaques is not linear, with phases of accelerated growth followed by quiescent periods. Pathology studies suggest that many plaque ruptures occur clinically silent.^{55,56} The anatomic hallmark of the layered plaque, suggestive of the plaque healing concept, is the presence of distinct layers of fibrotic tissue overlying areas with previous rupture or erosion.⁵⁷ In a series by Burke et al.,⁵⁶ 75% of ruptured plaques had evidence of previous ruptures, and cross-sectional lumen narrowing increased with the number of healed ruptures. Similar numbers of a multilayered phenotype were reported in OCT series by Wang et al.⁵⁸ and Dai et al.⁵⁹ Both layered culprit and nonculprit plaques were widespread. Layered plaques presented with more severe luminal stenosis at both culprit and nonculprit sites.⁵⁹ In line with these findings, Fracassi et al.⁶⁰ found, in an assessment of patients with ACS using OCT, that multilayered plaques presented with the most severe luminal narrowing compared with single-layered or nonlayered ones. An excellent diagnostic accuracy of OCT in the detection of healed plaques was confirmed in a co-registration study with histopathology by Shimokado et al.⁶¹

Of interest, several OCT studies concluded that a layered plaque pattern was more frequently observed in patients with a stable CAD presentation. It was hypothesized that patients with this phenotype would preferentially develop asymptomatic nonocclusive disruptions, leading to subsequent healing and plaque progression, rather than occlusive atherothrombotic events causing ACS.^{58,62}

Intraplaque Hemorrhage

As an alternative mode for the organization of mural thrombus after disruption of a plaque, sudden expansion of a plaque secondary to intraplaque hemorrhage is described, compatible with rapid stepwise progression of disease.⁶³ This is usually precipitated by neovessel rupture within the intima, causing blood extravasation leading to sudden enlargement in plaque size and corresponding luminal narrowing. Red blood cell membranes in the lipid core of the plaque contain a substantial amount of lipid, promoting recruitment of macrophages into the fibrous cap, further promoting plaque instability.⁶⁴

Effect of Intensive Statin Therapy

Optimal medical therapy with high-intensity statin improves clinical outcomes in patients with coronary atherosclerosis and induces plaque level changes detectable by imaging.⁶⁵ A meta-analysis by Ozaki et al.⁶⁶ showed that statin therapy induced a significant increase in fib FCT as assessed by OCT. In the Integrated Biomarker Imaging Study-4 (IBIS-4), IVUS and OCT of two non-infarct-related coronary arteries in the acute phase of 103 STEMI was performed. Patients were treated with high-dose rosuvastatin for 13 months. Serial OCT assessment revealed a significant increase in minimum FCT, reduction in macrophage accumulation, and frequent regression of TCFAs to other plaque phenotypes.⁶⁷

Etiology of the Acute Coronary Syndromes

Plaque rupture (45%–65%) and plaque erosion (30%–50%) are the dominant underlying mechanisms in patients with ACSs. Calcified culprit lesions are rarer and constitute 2% to 7% of cases in pathology as well as in clinical case series⁶⁸⁻⁷¹ ([Figure 17.7](#)). A common characteristic in these events is the occurrence of endothelial disruption, leading to platelet activation and thrombus formation, clinically presenting as ACS.⁷²

Ruptured Thin-Cap Fibroatheroma

Plaque rupture is defined as a defect or gap in the overlying cap of the fibroatheroma that leads to exposure of its highly thrombogenic substrates to the blood and is subsequently followed by rapid thrombus accumulation at the site of rupture.⁷³ Thrombi are often found overlying the ruptured segment. However, thrombus may be absent at the site of an old plaque rupture or with fresh rupture treated with antithrombotic or anticoagulant therapies.⁴⁰

Plaque Erosion

Plaque erosion tends to occur in younger patients, especially in premenopausal women. Current smoking is a predominant risk factor of plaque erosion, rather than dyslipidemia, hypertension, diabetes mellitus, or chronic kidney disease.⁷⁴ OCT data are consistent in showing that patients with plaque erosion more frequently present with non-ST-elevation myocardial infarction (NSTEMI) rather than with STEMI. Furthermore, patients with plaque

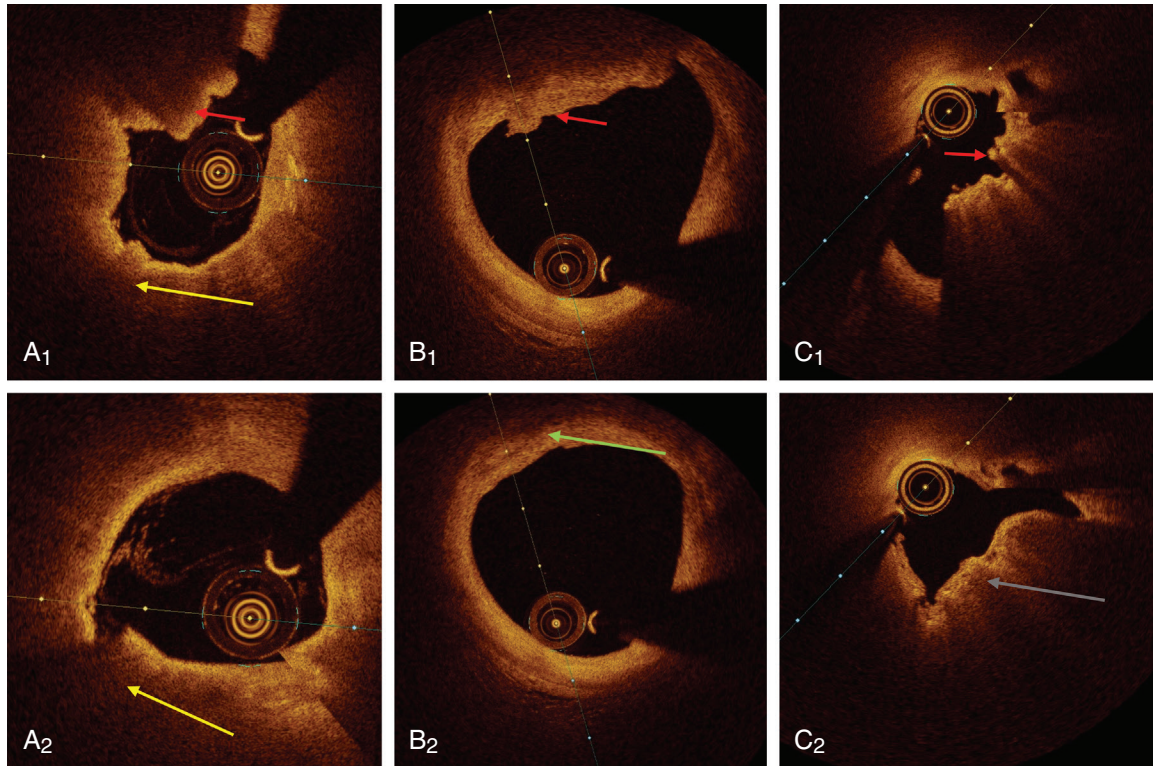


FIGURE 17.7 Etiology of acute coronary syndromes. **A₁**, Disrupted lipid-rich plaque. **B₁**, Plaque erosion. **C₁**, Calcified nodule with adjacent thrombus (red arrow). In **A₂**, **B₂**, and **C₂**, corresponding adjacent frames are shown, making more clear the underlying plaque morphology of the lesions: respectively, a lipid plaque (yellow arrow), a fibrous plaque (green arrow), and a calcified protrusion (gray arrow).

erosion have a significantly better clinical outcome, reflected in a lower incidence of major adverse cardiac events (MACEs) at follow-up compared with those with plaque rupture.⁷⁵

Endothelial denudation leads to the exposure of the proteoglycan and smooth muscle cell-rich intima.^{40,76} It is important to mention that detection of the endothelial monolayer (i.e., 1–5 μm) is below the resolution of the currently available OCT systems. Therefore, the OCT assessment of plaque erosion remains a diagnosis of exclusion, for which the combined observation of intraluminal thrombus and nondisrupted plaque is required.⁶⁸ An OCT diagnosis of plaque erosion is considered “definite” in the absence of fibrous cap disruption, in a lesion frequently composed of fibrous tissue, with overlying luminal white thrombus. The term “probable” OCT-erosion is coined when in the absence of clear luminal thrombus, an irregular luminal surface is observed, or if thrombus is observed, with attenuation of the underlying plaque, without evidence of superficial lipid or calcification in the vessel upstream or downstream of the thrombus site.⁶⁸ Previous pathology studies have reported that plaque erosion, compared with plaque rupture, had less “vulnerable” plaque features: smaller size of necrotic core, less inflammatory infiltration, fewer number of vasa vasorum, and a lower incidence of positive remodeling.^{69,76}

Higuma et al.⁷⁰ confirmed these findings in vivo with OCT: culprit plaque erosion in STEMI had fewer “vulnerable” plaque features than culprit plaque rupture did, including a lower prevalence of lipid plaque and TCFA, smaller size of lipid core, less frequent microchannels, and

a lower incidence of positive remodeling. In contrast, negative remodeling was more frequently observed in plaque erosion. STEMI caused by plaque erosion had a larger lumen cross-sectional area and smaller plaque burden at the culprit lesion site than plaque rupture did.⁷⁰

With the advent of intracoronary OCT and the opportunity it offers to diagnose plaque erosion as the culprit lesion in ACS patients, the hypothesis has been formulated to stabilize patients with plaque erosion with potent antithrombotic therapy without the need for coronary stenting.^{77,78} In the prospective Effective Anti-Thrombotic Therapy Without Stenting: Intravascular Optical Coherence Tomography-Based Management in Plaque Erosion (EROSION) study, 60 patients with ACS attributed to plaque erosion by OCT, with a residual vessel stenosis less than 70% and a TIMI (Thrombolysis in Myocardial Infarction) flow grade 3 on angiography, were enrolled. These patients were treated with potent antithrombotic therapy without stenting. Almost 80% of the enrolled patients showed a greater than 50% reduction of thrombus volume by OCT after 1 month, and more than one-third had no detectable thrombus.⁷⁷ A further reduction in thrombus volume was also shown between 1 month and 1 year, and the vast majority of these patients with plaque erosion managed “conservatively” remained free of major adverse cardiac events up to 1 year, although the study was underpowered in this regard.⁷⁹

The Calcified Culprit Plaque

The calcified culprit plaque is the least common, and as a consequence, the least investigated and understood of the

underlying causes of the ACSs. Recently, Sugiyama et al.⁸⁰ reported 1241 patients presenting with ACS who had undergone preintervention OCT. Among them, 157 (12.7%) patients were found to have a calcified plaque at the culprit lesion. Calcified plaque was defined as a plaque with superficial calcification at the culprit site without evidence of ruptured lipid plaque. The authors identified three distinctive types: eruptive calcified nodules, superficial calcific sheet, and calcified protrusion (prevalences of 25.5%, 67.4%, and 7.1%, respectively).⁸⁰ The intervention in patients presenting with calcified culprit plaque is challenging, mainly because the calcified burden poses additional challenges with respect to lesion preparation, where usually adjunctive measures such as the use of cutting or scoring balloons, rotational or orbital atherectomy, laser therapy, or lithotripsy are required before attempting stent implantation.

The Nonculprit Coronary Plaque in Acute Coronary Syndromes

Atherosclerotic disease is often observed in locations remote to the culprit plaque in patients presenting with ACS. Decisions for deferral of revascularization based on physiological assessment of nonculprit lesions are associated with a higher risk of future cardiovascular events in patients with ACS compared with those with stable angina.^{81,82} Adjunctive assessment with OCT holds the potential to identify vulnerable features at higher risk of future cardiovascular events in these patients.⁸³

In the COMPLETE (Complete vs Culprit-Only Revascularization to Treat Multi-Vessel Disease After Early PCI for STEMI)-OCT substudy, nearly 50% of patients had at least one obstructive nonculprit lesion containing complex vulnerable plaque. Obstructive lesions more commonly harbored vulnerable plaque morphology than nonobstructive lesions. The reduction of future events observed with complete revascularization in the COMPLETE trial suggests that nonculprit lesion PCI may effectively pacify these lesions.⁸⁴

Myocardial Infarction with Nonobstructive Coronary Atherosclerosis

Myocardial infarction with nonobstructive coronary atherosclerosis (MINOCA) is a syndrome with different causes, characterized by clinical evidence of MI with normal or mildly abnormal coronary arteries on angiography (stenosis severity <50%).

The mechanisms of MINOCA are multiple and have been classified as epicardial (epicardial spasm or unstable plaque not revealed by angiography) or microvascular (Takotsubo cardiomyopathy, myocarditis, microvascular spasm, distal microembolization).⁸⁵

Gerbaud et al.⁸⁶ used multimodality imaging with OCT and cardiac magnetic resonance in a series of patients with MINOCA and found evidence of plaque rupture, eruptive calcific nodule, plaque erosion, lone thrombus, and SCAD in 35%, 2.5%, 30%, 7.5%, and 5% of patients, respectively. In a similar assessment, Reynolds et al.⁸⁷ identified potential mechanisms in 84.5% of women with a diagnosis of MINOCA, three-quarters of which were ischemic and

one-quarter nonischemic. These studies provide evidence for performing OCT in cases of diagnostic uncertainty in the setting of ACS. By excluding atherosclerotic and thrombotic causes as the underlying cause of ACS, unnecessary lifelong treatments with antithrombotic or antiplatelet and antiatherosclerotic treatments can be avoided.⁸⁸

ROLE OF OPTICAL COHERENCE TOMOGRAPHY IN PERCUTANEOUS CORONARY INTERVENTION

Before Stent Deployment

Several studies have compared in vivo measurements of lumen area between IVUS and OCT. Bezerra et al.⁸⁹ reported comparable values of lumen area measured with both technologies in segments of the coronary artery that were free of disease, but at the site of minimum lumen area (MLA), lower values are measured with OCT compared with IVUS. It is hypothesized that a better delineation of the lumen border, especially in mixed or calcified plaques, could be responsible for these differences. These findings were confirmed in a similar study by Kubo et al.⁹⁰

Several studies have assessed the correlation between MLA measurements and functional assessment of intermediate lesions. Overall, these results are to be considered relatively disappointing. Intracoronary imaging, whether with IVUS or OCT, has only a moderate diagnostic efficiency in identifying severe coronary stenosis. In a large study by Gonzalo et al.,⁹¹ optimal MLA cutoff values for IVUS and OCT were 2.36 and 1.95 mm², respectively. The lower MLA value for OCT is consistent with lower values measured with OCT at the lesion site, probably because of a clearer delineation of the lumen contour. The low specificity of both imaging modalities precludes their use as a substitute for fractional flow reserve (FFR) with respect to the assessment of the indication for revascularization.

Traditionally, studies investigating stent sizing resulted in the choice for larger stent diameters with IVUS compared with OCT assessment.^{92,93} This relates to the fact that vessel sizing (media to media) was systematically used in IVUS studies compared with lumen diameters in the OCT assessment. Newer strategies using media to media assessments with OCT have been tested.^{94,95}

The criteria proposed in the Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN) III trial propose stent sizing based on the proximal and distal reference segment EEL measurements. If the EEL circumference is visible for 180 degrees or more, stent diameter is chosen by the smaller EEL diameter of the proximal or distal reference and rounded down to the nearest 0.25-mm stent diameter. If an EEL circumference 180 degrees or greater cannot be discriminated, stent sizing is based on lumen diameter (with rounding upward).⁹⁴

In addition to adequate stent sizing, OCT offers the unique opportunity to identify the extent of the lesion before stent implantation to allow for full lesion coverage ("from normal to normal") and potentially lower the risk of geographical miss,⁹⁶ which is a known predictor for both periprocedural MI and edge restenosis.⁹⁷⁻¹⁰⁰

Another aspect in the preprocedural work-up of coronary lesions is the assessment of the calcification burden in the coronary artery. Lesions with calcium deposits with maximum angle greater than 180 degrees, maximum thickness greater than 0.5 mm, and length longer than 5 mm have been reported to be at a higher risk of stent underexpansion⁹⁴ and would probably benefit from more aggressive plaque modification before stent implantation. It is important to mention that stent deployment without adequate pretreatment often leads to underexpansion, persisting even after aggressive postdilation.

Recently, intravascular lithotripsy has been proposed as a new strategy for modification of the calcified plaque and a valuable alternative for earlier established therapies such as cutting or scoring balloons, noncompliant balloons and rotational or orbital atherectomy. Evidence with respect to procedural safety, efficacy, and cracking of the calcified plaque have been provided by a series of clinical trials (Disrupt Coronary Artery Disease [CAD] II, III, and IV), including assessment with OCT.¹⁰¹⁻¹⁰³

Bifurcation Intervention

The challenges of coronary intervention, with respect to stent sizing and positioning and optimization after stent implantation, are amplified when dealing with the bifurcation lesion. The use of OCT offers important insights leading to correct sizing according to the distal main vessel anatomy, exact positioning of the stent over the bifurcation segment, and selection of the appropriate size of the balloon for effective execution of the proximal optimization technique (POT). Some pioneering studies investigate the adjunctive role of OCT in selecting the most optimal cell opening toward the side branch, ensuring optimal coverage of the side branch ostium while minimizing at the same time the accumulation of metal at the carina level.¹⁰⁴⁻¹⁰⁶ This concept is currently being further investigated in the On-line 3-dimensional Optical Frequency Domain Imaging to Optimize Bifurcation Stenting Using UltiMaster Stent (OPTIMUM) (NCT02972489) randomized trial.¹⁰⁷ Perhaps the most important added value of OCT in the specific setting of bifurcation intervention is its capability of checking the correct position of the wire used for recrossing into the side branch after the main vessel stent is positioned. Even after a POT maneuver with an adequately sized balloon, there remains a substantial risk for the newly positioned wire to go underneath some struts of the proximal main vessel stent.¹⁰⁸ This can lead to excessive distortion of the proximal main vessel stent when a balloon is passed over this wire and dilated toward the side branch. The damage (huge stent deformation) provoked in the proximal part of the stented segment cannot be detected by routine angiography. The adjunctive role of OCT in coronary bifurcation intervention (including left main lesions) is currently being investigated in the OCTOBER study.¹⁰⁹

Angiographic assessment of the left main coronary artery (LMCA) by angiography alone is difficult. Specifically, not only is the angiographic assessment of lesion severity most variable in the LMCA, but also sizing is more difficult than in any other coronary vessel.¹¹⁰ Fujino et al.¹¹¹

reported that guiding LMCA stenting by OCT was feasible and safe and provided superior information on stent position compared with IVUS but was limited in ostial LMCA assessment. Burzotta et al.¹¹² confirmed that OCT evaluation was feasible in midshaft and distal LMCA lesions. The French LEft Main Oct-guided iNterventions (LEMON) study investigated the feasibility and performance of OCT-guided left main stem PCI according to a prespecified protocol, with promising results.¹¹³

Immediate Poststent Deployment

In line with accruing evidence on the use of intracoronary imaging, recent European guidelines have enforced their recommendation for the use of intracoronary imaging (with IVUS or OCT) for stent optimization after PCI to a Class IIa Level of evidence B (<https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/ESC-EACTS-Guidelines-in-Myocardial-Revascularisation-Guidelines-for>).¹¹⁴

The benefit of IVUS-guided PCI has been established through a series of randomized controlled trials and meta-analyses.¹¹⁵⁻¹¹⁷ The additional value was especially observed in more complex patient and lesion subsets such as left main and bifurcation lesions and long lesions and patients presenting with ACS.¹¹⁷

Being a much younger technology, the evidence with respect to the clinical benefit of OCT guided PCI is scarcer. Compared with IVUS, there are some limitations such as the need for clearing the vessel of blood and the additional contrast load and limitations in the ability to make optimal assessment of subtotal lesions and lesions of the ostial left main stem. In contrast, OCT has a much better image resolution compared with IVUS and measures luminal and stent dimensions more accurately.⁹⁰ Several characteristics, such as stent apposition, edge dissection, tissue protrusion, and the presence of thrombus, can be assessed with much more detail using OCT (Figure 17.8.).

In the Centro per la Lotta contro l'Infarto–Optimisation of Percutaneous Coronary Intervention (CLI-OPCI) study, a nonrandomized, retrospective comparison of 335 OCT-guided PCI cases with 335 angiography-guided PCI cases, OCT identified complications requiring further intervention in one-third of patients, and a lower risk of cardiac death and MI was observed.¹¹⁸ Although intriguing, these results would need confirmation in randomized controlled studies to firmly establish a clinical benefit to OCT-guided PCI.

In the Does Optical Coherence Tomography Optimize Results of Stenting (DOCTORS) study, a multicenter randomized trial comparing OCT-guided with angiography-guided PCI in 240 patients with non-ST-segment elevation ACS, post-PCI FFR and the prevalence of post-PCI FFR greater than 0.9 were significantly higher in the OCT-guided group compared with the angiography-guided group. The use of OCT led to PCI optimization in a substantial amount of cases, with marked improvement in post PCI stent expansion measures.¹¹⁹ In the randomized OPINION (Optical Frequency Domain Imaging vs. Intravascular Ultrasound in Percutaneous Coronary Intervention) trial, target vessel failure was noninferior by OCT compared with IVUS (5.2% vs 4.9%; P noninferiority = .04). Stent diameter was chosen based on reference lumen diameter by OCT and reference

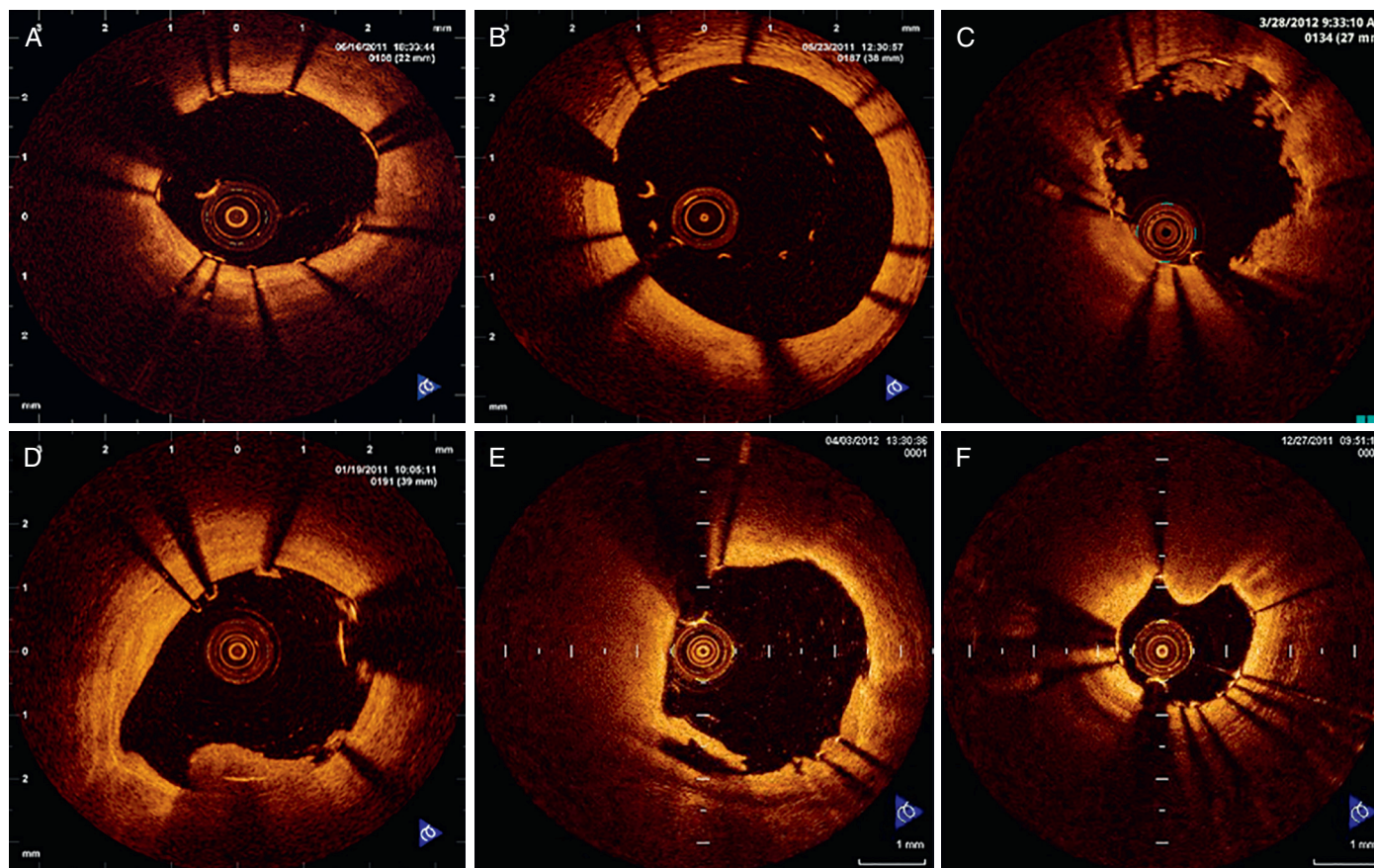


FIGURE 17.8 Optical coherence tomography images immediately after percutaneous coronary intervention. **A**, Well-apposed stent. **B**, Severely malapposed stent. **C**, Acute stent thrombosis. **D**, Mural thrombus. **E**, Edge dissection. **F**, Tissue prolapse.

vessel diameter (EEL) by IVUS. Although the difference was minimal, the chosen stent size was significantly smaller in the OCT arm compared with the IVUS arm.⁹³

In the prospective, randomized ILUMIEN III trial,⁹⁴ 450 patients (the majority with noncomplex lesions) were randomized to OCT vs IVUS versus angiography-guided PCI. A novel OCT-based stent sizing strategy using reference segment EELs was used. The primary efficacy endpoint was post-PCI luminal dimension, the minimal stent area (MSA). OCT guidance appeared to be noninferior but not superior to IVUS guidance. OCT guidance was not superior to angiography guidance for MSA but did lead to greater stent expansion. OCT guidance also led to fewer cases of major dissection and major malapposition than IVUS guidance and angiography guidance.

In the OCT guidance arm, EEL visibility of 180 degrees or greater was apparent in 69% of proximal and 77% of distal reference segments by the operator, and stent size was based on EEL diameters for almost all these cases. In a core laboratory setting, distal EEL diameter could be measured in 95% of cases, which indicates the potential for improvement in the clinical setting.

Several larger randomized trials are currently ongoing, exploring further the adjunctive role of OCT in optimization of PCI. In the ILUMIEN IV trial (NCT03507777),⁹⁵ 2487 patients with diabetes or with complex coronary lesions have been enrolled and randomized between an OCT-guided and an angiography-guided PCI strategy. The

primary endpoint is improvement in post-PCI lumen dimensions, with several clinical outcomes as secondary outcome measures. In the Optical Coherence Tomography Versus Intravascular Ultrasound Guided Percutaneous Coronary Intervention (OCTIVUS) trial (NCT03394079), a multicenter randomized Korean 2000-patient trial, OCT-versus IVUS-guided PCI are compared, with the use of common algorithms for IVUS and OCT. The primary endpoint is target vessel failure at 1 year.¹²⁰ Finally, in the Japanese Comparison Between Optimal Coherence Tomography Guidance and Angiography Guidance in Percutaneous Coronary Intervention (COCOA) trial, (NCT03176810), 550 patients are randomized to OCT vs angiography guided PCI. The primary endpoint is MSA post PCI.¹²¹

Stent Expansion

Stent expansion is by far the most important parameter to assess after stent implantation, and so far, after correction, the only one to be associated with improved clinical outcome.¹²²⁻¹²⁵

Metal stent struts are highly reflective and generate a strong signal with shadowing behind the stent strut (“blooming”). Although different definitions and cutoffs have been applied in clinical research over the past years,¹²⁶ it is currently accepted to define adequate stent expansion by OCT as a minimal in-stent lumen area that is 90% or more of the mean of the proximal and distal reference

vessel lumen area. To accommodate for vessel tapering in long lesions, the protocol used in the ILUMIEN III and IV studies prescribed to divide longer stented segments into proximal and distal halves. In the post-PCI OCT assessment, the MSA of each half is compared with the respective reference lumen area, with again 90% or more considered acceptable stent expansion⁹⁴ (Figure 17.9).

Malapposition

Immediately after intervention, individual stent struts are either apposed or malapposed. Apposed stent struts are further classified as embedded or protruding. Struts buried in the vessel wall by more than half of the strut thickness are defined as embedded. Struts with the adluminal stent strut surface above the luminal surface of the vessel wall are defined as protruding.¹²⁷ The distance from the stent strut to the vessel wall is measured, and if this value is greater than the nominal stent strut thickness, the stent strut is classified as malapposed. For DESs, the distance includes the sum of the strut thickness and the thickness of the abluminal polymer. The extent of malapposition is determined by the number of cross sections containing malapposed struts. Compatible with its higher resolution, malapposition (especially minor degrees of malapposition) is detected much more often with OCT than with IVUS.⁹⁴ In the absence of underexpansion, there is no association with adverse early or long-term outcomes for acute malapposition.^{124,125,128,129} However, several OCT registries investigating cases of stent thrombosis have documented an

association between the presence of malapposition and the occurrence of stent thrombosis, in early, late as well as very late stent thrombosis cases.¹³⁰⁻¹³² In the Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort (PRESTIGE) study, frank malapposition was a common finding in cases of acute stent thrombosis.¹³⁰ The extent of malapposition seems to be an important parameter, with Taniwaki et al.¹³ reporting a link between the longitudinal extent of malapposition and the risk of stent thrombosis and Kim et al.¹³³ observing an association between total malapposition volume and adverse outcome.

Edge Dissection

Edge dissection is a common finding in OCT acquisitions. Given its higher resolution compared with IVUS, edge dissection is much more easily detected when using OCT. However, it is generally accepted that only frank edge dissection needs to be treated with additional stent implantation. In the Centro per la Lotta contro l'Infarto–Optimisation of Percutaneous Coronary Intervention (CLI-OPCI) trial, important residual edge stenosis could be withheld as a strong predictor of MACE.¹¹⁸ In the Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents (ADAPT-DES) trial (using IVUS), lumen area within the dissection smaller than 5.0 mm², dissection length longer than 3 mm, and dissection flap radial extent greater than 60 degrees were criteria associated with an increased risk of target vessel revascularization.¹³⁴ These findings were integrated in the ILUMIEN III OCT criteria for the treatment of edge dissection.⁹⁴

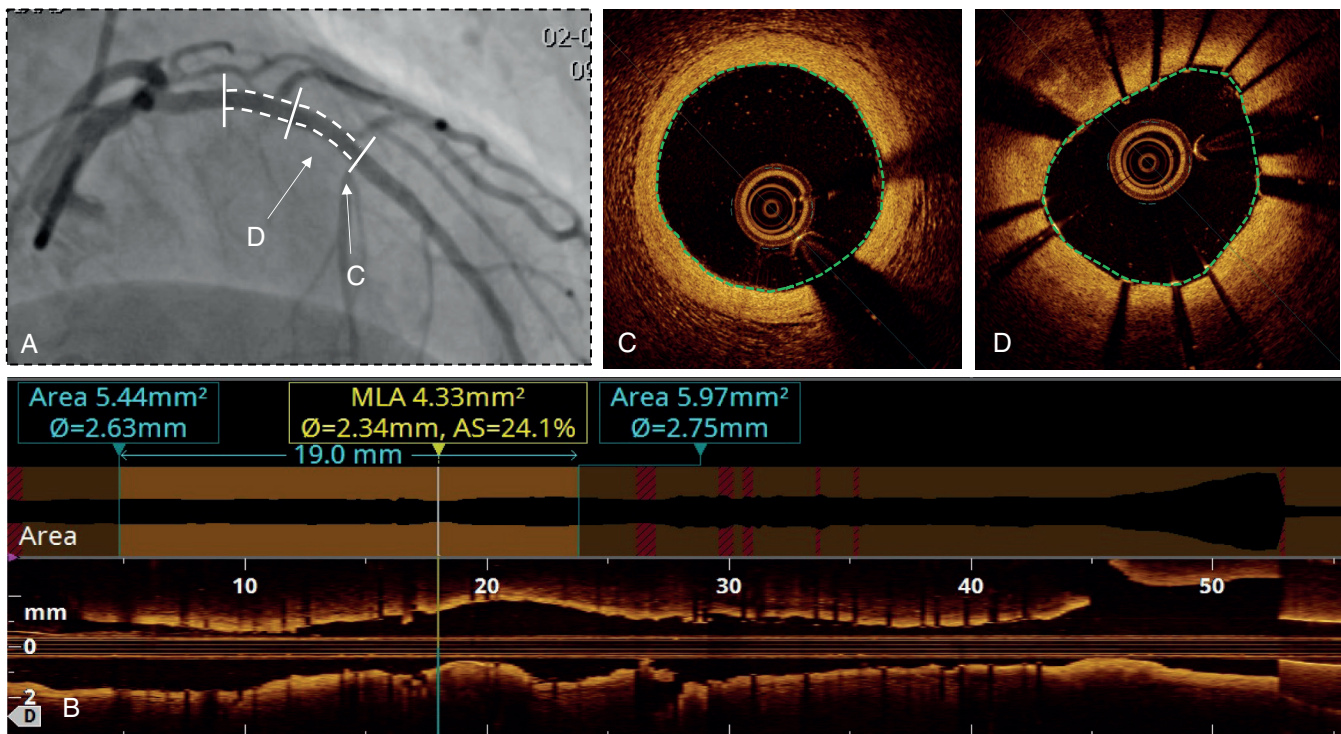


FIGURE 17.9 Assessment of stent expansion according to ILUMIEN III criteria. The stented segment is divided automatically into a proximal and a distal half. In the distal half, the minimal stent area is detected and determined to be 4.33 mm². This value is compared with the mean of the distal reference area (5.4 mm²) and the stent area in the midposition of the stent (5.97 mm²). This gives a stent expansion of 76%, which would clearly lead to a recommendation of additional postdilation, in an attempt to achieve at least 90% stent expansion. **A**, coronary angiogram of mid left anterior descending (LAD) stented segment. **B**, longitudinal OCT view. **C**, distal reference area. **D**, measurement of minimal stent area. *MLA*, Minimum Lumen Area.

Tissue Protrusion

Tissue protrusion is a common finding in post-PCI OCT and IVUS pullbacks. Its clinical significance is not completely understood, however. Although minor tissue protrusion can be considered a benign bystander,¹³⁵ irregular protrusion (probably representing deep vascular injury) is associated with target vessel failure and early stent thrombosis.^{124,128}

Late Stent Evaluation

In long-term follow-up of stents, stent strut apposition, tissue coverage, and extent of neointimal growth are key intermediate endpoints in comparing various stent platforms (Figure 17.10).¹³⁶ Stent strut coverage is of particular importance because of the association between the absence of neointimal stent coverage and late stent thrombosis.¹³⁷ Similar to the immediate postintervention time-point, stent struts at follow-up can be classified as embedded, protruding, or malapposed. Malapposition, or lack of contact between stents and intima, appears to correlate with stent failure.^{138,139} Serial OCT studies have shown that inadequate stent deployment during the index PCI procedure is the most common cause of late stent malapposition.¹⁴⁰ Late-acquired stent malapposition in stents that were adequately apposed immediately after PCI is most frequently associated with significant plaque or thrombus prolapse immediately after intervention (see Figure 17.10C).

Stent struts can be covered or uncovered by neointima (see Figure 17.10A and B). Ideally, a coronary stent would allow for a thin layer of stent coverage without significant neointimal hyperplasia, which could proceed to in-stent

restenosis. The interest in the study of arterial healing following DES implantation is based on autopsy studies reporting a higher frequency of uncovered stent struts per section in cases of late DES thrombosis compared with control participant.¹³⁷ With OCT, the evaluation of tissue coverage above stent struts has become feasible in an in vivo setting, confirming the association between uncovered struts and stent thrombosis.¹⁴¹ Although a direct causality has never been proven, incomplete stent strut coverage is traditionally regarded as a meaningful indicator of an increased thrombotic risk.¹⁴² However, the inability to characterize the composition of the tissue covering stent struts, specifically distinguishing cellular coverage from fibrinous material, is a limitation in the use of OCT to evaluate strut coverage. This is an important distinction because excess fibrin deposition has been linked to late stent thrombosis in autopsy studies.¹⁴³

Optical coherence tomography has had a primary role as an investigational tool to compare various stent platforms through the evaluation of stent strut coverage. Specifically, because stent thrombosis, the most feared post-PCI complication, is relatively rare, it cannot reliably be used as a study endpoint in the context of most randomized trials. OCT has provided a valuable surrogate endpoint, stent strut coverage, that made randomized studies comparing new stent designs and drug-elution kinetics feasible.^{21,144,145}

Neoatherosclerosis

Beyond describing the extent of tissue coverage, OCT can identify the tissue composition of the material causing

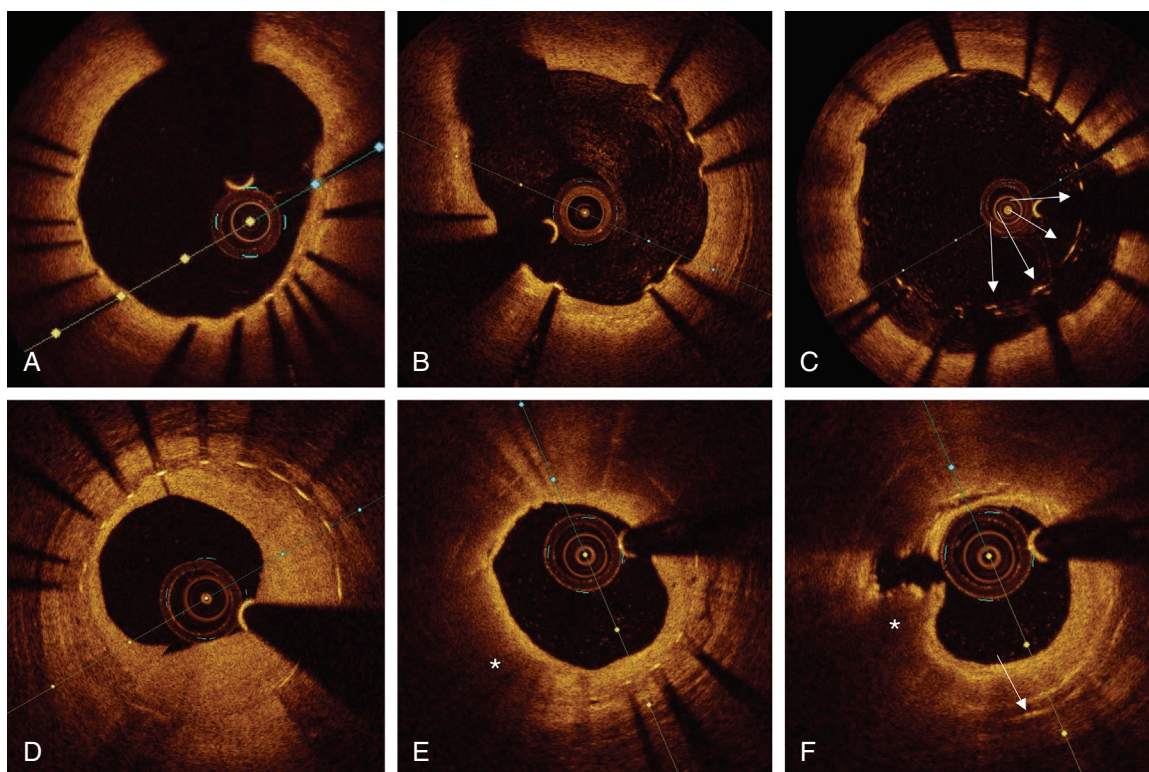


FIGURE 17.10 Optical coherence tomography follow-up imaging of coronary stents. **A**, Well-apposed and covered stents. **B**, Well-apposed but uncovered stents. **C**, Malapposed stent struts (white arrows). **D**, Homogeneous in-stent. **E**, In-stent restenosis with neoatherosclerosis and lipid-laden plaque (asterisk). **F**, Ruptured neoatherosclerotic plaque (asterisk) inside a previously placed stent (arrow).

in-stent restenosis (see Figure 17.10D and E). In-stent restenosis secondary to smooth muscle cell proliferation has a homogeneous appearance and a smooth lumen contour when imaged with OCT.¹⁴⁶ Neoatherosclerosis is pathologically distinct from neointimal hyperplasia. Histologically, the hallmark of in-stent neoatherosclerosis is the accumulation of lipid-laden macrophage foam cells in the neointimal tissue of the stented segment, with or without necrotic core formation or calcification within the neointima.¹⁴⁷ Neoatherosclerosis is an accelerated process compared with atherosclerosis in native vessels, and its time course appears to be affected by implanted device type. Neoatherosclerosis within the stent is characterized by the presence of calcification and lipid pools within the intima and formation of fibroatheromas. Similar to coronary atherosclerosis, neoatherosclerosis can result in the formation of TCFA with lipid-rich neointima and a thin fibrous cap.¹⁴⁸ Macrophage infiltration and formation of microvessels have also been reported within neoatherosclerotic lesions.^{149,150} Pathological studies have shown a distinct time course for the formation of neoatherosclerosis in bare-metal stents (BMSs) and DESs. Within 6 months of BMS placement, smooth muscle cell proliferation results in the development of neointima visualized as a homogeneous OCT signal overlying the stent struts.¹⁵¹ The OCT findings of neoatherosclerosis were first reported by Takano et al.¹⁵² in 2009. Neoatherosclerosis is not seen before 2 years after BMS implantation and typically not until 4 years after implantation.¹⁴⁸ In contrast, neoatherosclerosis is seen after 1 year of PCI with DES. OCT studies have shown similarly distinct time courses for neoatherosclerosis in BMSs versus DESs.^{150,152,153} The degrees of neointimal hyperplasia, smoking history, chronic kidney disease, and use of DESs appear to be associated with the formation of neoatherosclerosis.^{149,154}

Disruption of TCFA present within the neointima can lead to ACS and may potentially explain a subset of cases with very late stent thrombosis (see Figure 17.10F).¹⁵⁵ These findings have been corroborated by pathology and IVUS studies and may help identify a potential novel mechanism of late stent failure.^{156,157}

Stent Thrombosis

Optical coherence tomography has been established as an important tool in the assessment of stent failure (stent

thrombosis and in-stent restenosis), both in the setting of individual case management and in clinical research (Figure 17.11).

After multiple case reports and smaller series on the underlying mechanism of stent thrombosis, three large OCT registries on this topic have been published.¹³⁰⁻¹³² Although the studies varied in the types of stent thrombosis that were included (early vs late vs very late stent thrombosis) and the methodology used to assess the OCT acquisitions, important parallels between the conclusions of the different reports can be made. Malapposition and underexpansion are important underlying mechanisms in early stent thrombosis, suggesting a role for PCI optimization measures. In very late stent thrombosis (occurring >1 year after stent implantation), neoatherosclerosis (with or without rupture) was confirmed as a very common underlying mechanism as defined by OCT. Other mechanisms include the persistence of uncovered struts, malapposition, stent underexpansion and severe in-stent restenosis. In general, it remains important to keep in mind that the studies mentioned are registries of cases of stent thrombosis, not prospective studies on the outcome of PCI. Therefore, the findings of these studies reflect an association between the observations and the occurrence of stent thrombosis and not necessarily a causal relationship.

Use of OCT in cases of stent thrombosis leads to an important decrease in the percentage of operator-defined “unidentified mechanism of stent thrombosis” from 48% by angiography alone to 13% by OCT.¹³¹ The use of additional stents (31%) was half compared with a large angiography-guided stent thrombosis cohort (63.5%).¹⁵⁸

In-Stent Restenosis

With respect to the clinical investigation of in-stent restenosis, important parallels can be observed. In patients with second-generation DES restenosis occurring within the first year after implantation evaluated by OCT, the dominant cause was stent underexpansion (MSA <4 mm² and neointimal hyperplasia <50% of stent area) in 40% of cases. Neoatherosclerosis is commonly observed in cases of very late in-stent restenosis, and in a substantial proportion of cases of stent thrombosis, an overlap phenomenon is observed, imaged as severe restenosis with superimposed thrombus

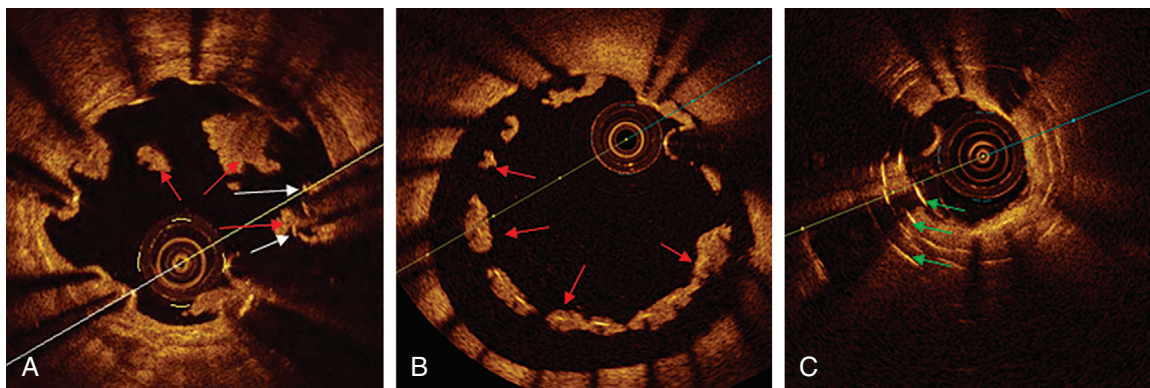


FIGURE 17.11 **A**, In-stent thrombosis caused by persistence of uncovered and malapposed stent struts (white arrows). **B**, Stent thrombosis caused by malapposition. There is thrombus adjacent to the malapposed struts (red arrows). **C**, Stent thrombosis caused by underexpansion in a region with multiple overlapping stents (green arrows).



and clinically presenting as ACS. In a minority of patients presenting with in-stent restenosis, a calcified nodule-like in-stent restenosis is observed, appearing as a high-back-scattering protruding mass with an irregular surface covered by signal-rich bands. This specific type can be observed in around 10% of cases of in-stent restenosis, especially within stents deployed in severely calcified lesions.¹⁵⁹

The investigation of in-stent restenosis with OCT can add important insights into the underlying causes of this form of stent failure. When reintervening on an in-stent restenotic lesion, preexisting stent underexpansion, the amount of neointimal calcium, and the presence of multiple old stent strut layers have been identified as important determinants of new stent underexpansion, which would lead to further future adverse events.¹⁶⁰

Transplant Vasculopathy

Cardiac allograft vasculopathy is the primary cause of late graft failure in heart transplant recipients. It remains a diagnostic challenge because patients often lack signs and symptoms early in the disease process caused by cardiac denervation. Angiography remains the standard screening diagnostic test but is limited at identifying graft vasculopathy because of the diffuse rather than focal nature of the disease. OCT has been found to be significantly more sensitive at identifying intimal hyperplasia, an early manifestation of allograft vasculopathy, than angiography or IVUS.¹⁶¹

FUTURE DIRECTIONS

Combined Morphologic and Functional Assessment

Currently, it is a common practice for operators to switch between functional (using FFR or nonresting flow indices) and morphologic (intracoronary imaging using IVUS, OCT, or both) assessment of patients.¹⁶² Whereas the functional assessment is predominantly used to define the indication for revascularization, OCT assessment is implied for planning the procedure and for PCI optimization. The combined Abbott Vascular ILUMIEN system allows for assessment of both OCT and FFR/RFR by using a single console.

Optical flow ratio (OFR) is a novel method for computation of fractional flow reserve from OCT images with an overall vessel-level diagnostic accuracy of 90% and sensitivity and specificity of 87% and 92%, respectively.¹⁶³ These values are superior to what can be achieved using single MLA values because OFR holds the potential to integrate additional lesion characteristics (e.g., lesion length and plaque eccentricity) along the interrogated vessel into the computation of pressure drop.

Multimodality Systems

Different modalities of intracoronary imaging each have strengths and weaknesses. The morphologic detail of OCT is unsurpassed. However, penetration depth is limited to the first few millimeters of the coronary artery wall. This limitation can be overcome by combined IVUS and OCT

imaging catheters, which have shown an increase in diagnostic performance.^{51,164} Combined IVUS-near-infrared spectroscopy (NIRS) imaging catheters have proven their efficacy in improving the diagnostic accuracy of characterization of the lipid component of plaques. Similar improvements in lipid characterization capacities could be expected from the combination of OCT and NIRS¹⁶⁵ or OCT and autofluorescence technologies.^{166,167}

Micro-optical Optical Coherence Tomography

Current OCT systems with a resolution of approximately 10 μm cannot visualize cellular and subcellular structures. An OCT system with significantly higher resolution (1–2 μm) has been reported that may allow for resolution of single cells and potentially subcellular structures within coronary vasculature.¹⁶⁸ Imaging of cadaveric arteries readily identified endothelial cells, adherent leukocytes and macrophages, cholesterol crystals, and microcalcifications. Recently, a single fiberoptic μOCT probe and intracoronary catheter have been created, which should bring the clinical in vivo application of μOCT technology within reach.¹⁶⁹ This could enable an understanding of endothelial cell function in the early phases of plaque development, plaque disruption and progression, and specific aspects of stent healing and failure.¹⁷⁰

CONCLUSION

Optical coherence tomography is a real-time intravascular imaging technology that currently provides unmatched high-resolution images of superficial intracoronary structures including coronary plaques and stents. As a research tool, OCT has an established role in helping understand coronary pathology and vascular response to injury and stenting. With improvements in the ease of use and the expansion of the number of trained operators and teams, the potential exists for the regular use of OCT in guiding PCI, especially during complex coronary intervention and after stent thrombosis. The results of several ongoing randomized trials will be of primary importance for the technology to definitively establish its role in the setting of guidance of intervention and PCI optimization.

SUMMARY

Optical coherence tomography is a tomographic imaging technology allowing real-time ultra-detailed intravascular imaging. Current-generation FD-OCT, using a nonocclusive contrast flushing method to create a blood-free zone combined with faster catheter pullback, allow for straightforward image acquisition. Among others, OCT allows for the in vivo assessment of the layered plaque, TCFA, plaque erosion, and ruptured calcified nodules. This has considerably advanced our insights in the pathobiology of the coronary plaque and the mechanisms underlying plaque progression and the occurrence of ACSs. OCT has been very important in our understanding of the healing process after intracoronary stent implantation and the mechanism un-

derlying DES and bioresorbable scaffold failure. Currently, several large, randomized trials are investigating the adjunctive role of OCT in optimization of PCI procedures, with a special focus on more complex lesion subsets.

Dual-modality imaging (the combination of OCT with modalities such as NIRS and autofluorescence), micro OCT, the computation of functional data based on detailed OCT images, and the introduction of OCT in other vascular territories (e.g., the cerebral vasculature) hold promise for further advancements in the field.

Visit Elsevier eBooks + to access the complete list of references

SELECTED REFERENCES

18. Min HS, Yoo JH, Kang SJ, et al. Detection of optical coherence tomography-derived thin-cap fibroatheroma in the coronary artery using deep learning. *EuroIntervention*. 2020;16:404-412.
21. Tearney GJ, Regar E, Akasaka T, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol*. 2012;59:1058-1072.
35. Katayama Y, Tanaka A, Taruya A, et al. Feasibility and clinical significance of in vivo cholesterol crystal detection using optical coherence tomography. *Arterioscler Thromb Vasc Biol*. 2020;40:220-229.
50. Brown AJ, Obaid DR, Costopoulos C, et al. Direct comparison of virtual-histology intravascular ultrasound and optical coherence tomography imaging for identification of thin-cap fibroatheroma. *Circ Cardiovasc Imaging*. 2015;8:e003487.
51. Fujii K, Hao H, Shibuya M, et al. Accuracy of OCT, grayscale IVUS, and their combination for the diagnosis of coronary TCFA: an ex vivo validation study. *JACC Cardiovasc Imaging*. 2015;8:451-460.
57. Vergallo R, Crea F. Atherosclerotic plaque healing. *N Engl J Med*. 2020;383:846-857.
58. Wang C, Hu S, Wu J, et al. Characteristics and significance of healed plaques in patients with acute coronary syndrome and stable angina: an in vivo OCT and IVUS study. *EuroIntervention*. 2019;15:e771-e778.
59. Dai J, Fang C, Zhang S, et al. Frequency, predictors, distribution, and morphological characteristics of layered culprit and nonculprit plaques of patients with acute myocardial infarction: in vivo 3-vessel optical coherence tomography study. *Circ Cardiovasc Interv*. 2020;13:e009125.
60. Fracassi F, Crea F, Sugiyama T, et al. Healed culprit plaques in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2019;73:2253-2263.
61. Shimokado A, Matsuo Y, Kubo T, et al. In vivo optical coherence tomography imaging and histopathology of healed coronary plaques. *Atherosclerosis*. 2018;275:35-42.
62. Vergallo R, Porto I, D'Amario D, et al. Coronary atherosclerotic phenotype and plaque healing in patients with recurrent acute coronary syndromes compared with patients with long-term clinical stability: an in vivo optical coherence tomography study. *JAMA Cardiol*. 2019;4:321-329.
64. Kolodgie FD, Gold HK, Burke AP, et al. Intraplaque hemorrhage and progression of coronary atheroma. *N Engl J Med*. 2003;349:2316-2325.
67. Räber L, Koskinas KC, Yamaji K, et al. Changes in Coronary plaque composition in patients with acute myocardial infarction treated with high-intensity statin therapy (IBIS-4): a serial optical coherence tomography study. *JACC Cardiovasc Imaging*. 2019;12:1518-1528.
68. Jia H, Abtahian F, Aguirre AD, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol*. 2013;62:1748-1758.
69. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol*. 2006;47:C13-C18.
70. Higuma T, Soeda T, Abe N, et al. A combined optical coherence tomography and intravascular ultrasound study on plaque rupture, plaque erosion, and calcified nodule in patients with ST-segment elevation myocardial infarction: incidence, morphologic characteristics, and outcomes after percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2015;8:1166-1176.
71. Lee T, Mintz GS, Matsumura M, et al. Prevalence, predictors, and clinical presentation of a calcified nodule as assessed by optical coherence tomography. *JACC Cardiovasc Imaging*. 2017;10:883-891.
74. Dai J, Xing L, Jia H, et al. In vivo predictors of plaque erosion in patients with ST-segment elevation myocardial infarction: a clinical, angiographical, and intravascular optical coherence tomography study. *Eur Heart J*. 2018;39:2077-2085.
75. Niccoli G, Montone RA, Di Vito L, et al. Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome. *Eur Heart J*. 2015;36:1377-1384.
77. Jia H, Dai J, Hou J, et al. Effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based management in plaque erosion (the EROSION study). *Eur Heart J*. 2017;38:792-800.
80. Sugiyama T, Yamamoto E, Fracassi F, et al. Calcified plaques in patients with acute coronary syndromes. *JACC Cardiovasc Interv*. 2019;12:531-540.
83. Montone RA, Niccoli G, Crea F, Jang IK. Management of non-culprit coronary plaques in patients with acute coronary syndrome. *Eur Heart J*. 2020;41:3579-3586.
84. Pinilla-Echeverri N, Mehta SR, Wang J, et al. Nonculprit lesion plaque morphology in patients with ST-segment-elevation myocardial infarction: results from the COMPLETE trial optical coherence tomography substudy. *Circ Cardiovasc Interv*. 2020;13(7):e008768.
86. Gerbaud E, Arabucki F, Nivet H, et al. OCT and CMR for the diagnosis of patients presenting with MINOCA and suspected epicardial causes. *JACC Cardiovasc Imaging*. 2020;13:2619-2631.
93. Kubo T, Shinke T, Okamura T, et al. Optical frequency domain imaging vs. intravascular ultrasound in percutaneous coronary intervention (OPINION trial): one-year angiographic and clinical results. *Eur Heart J*. 2017;38:3139-3147.
94. Ali ZA, Maehara A, Généreux P, et al. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (LUMIEN III: OPTIMIZE PCI): a randomised controlled trial. *Lancet*. 2016;388:2618-2628.
95. Ali Z, Landmesser U, Karimi Galougahi K, et al. Optical coherence tomography-guided coronary stent implantation compared to angiography: a multicentre randomised trial in PCI - design and rationale of ILUMIEN IV: OPTIMAL PCI. *EuroIntervention*. 2021;16:1092-1099.
109. Holm NR, Andreasen LN, Walsh S, et al. Rational and design of the European randomized Optical Coherence Tomography Optimized Bifurcation Event Reduction Trial (OCTOBER). *Am Heart J*. 2018;205:97-109.
114. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
123. Fujii K, Carlier SG, Mintz GS, et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol*. 2005;45:995-998.
124. Soeda T, Uemura S, Park SJ, et al. Incidence and clinical significance of poststent optical coherence tomography findings: one-year follow-up study from a multicenter registry. *Circulation*. 2015;132:1020-1029.
130. Adriaenssens T, Joner M, Godschalk TC, et al. Optical coherence tomography findings in patients with coronary stent thrombosis: a report of the PRESTIGE Consortium (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort). *Circulation*. 2017;136:1007-1021.
131. Souteyrand G, Amabile N, Mangin L, et al. Mechanisms of stent thrombosis analysed by optical coherence tomography: insights from the national PESTO French registry. *Eur Heart J*. 2016;37:1208-1216.
132. Taniwaki M, Radu MD, Zaugg S, et al. Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. *Circulation*. 2016;133:650.
137. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation*. 2007;115:2435-2441.
142. Räber L. Short DAPT duration for well-covered stents? *JACC Cardiovasc Imaging*. 2018;11:1820-1822.
148. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol*. 2011;57:1314-1322.
153. Yonetsu T, Kim JS, Kato K, et al. Comparison of incidence and time course of neoatherosclerosis between bare metal stents and drug-eluting stents using optical coherence tomography. *Am J Cardiol*. 2012;110:933-939.
166. Ughi GJ, Verjans J, Fard AM, et al. Dual modality intravascular optical coherence tomography (OCT) and near-infrared fluorescence (NIRF) imaging: a fully automated algorithm for the distance-calibration of NIRF signal intensity for quantitative molecular imaging. *Int J Cardiovasc Imaging*. 2015;31:259-268.

REFERENCES

- Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science*. 1991;254:1178-1181.
- Takada K, Yokohama I, Chida K, Noda J. New measurement system for fault location in optical waveguide devices based on an interferometric technique. *Appl Opt*. 1987;26:1603-1606.
- Youngquist RC, Carr S, Davies DE. Optical coherence-domain reflectometry: a new optical evaluation technique. *Opt Lett*. 1987;12:158-160.
- Tearney GJ, Brezinski ME, Bouma BE, et al. In vivo endoscopic optical biopsy with optical coherence tomography. *Science*. 1997;276:2037-2039.
- Bouma BE, Yun SH, Vakoc BJ, Suter MJ, Tearney GJ. Fourier-domain optical coherence tomography: recent advances toward clinical utility. *Curr Opin Biotechnol*. 2009;20:111-118.
- Herrero-Garibi J, Cruz-González I, Parejo-Díaz P, Jang IK. Optical coherence tomography: its value in intravascular diagnosis today. *Rev Esp Cardiol*. 2010;63:951-962.
- Suh WM, Seto AH, Margey RJ, Cruz-Gonzalez I, Jang IK. Intravascular detection of the vulnerable plaque. *Circ Cardiovasc Imaging*. 2011;4:169-178.
- Ughi GJ, Marosfoi MG, King RM, et al. A neurovascular high-frequency optical coherence tomography system enables in situ cerebrovascular volumetric microscopy. *Nat Commun*. 2020;11:3851.
- van der Sijde JN, Karanasos A, van Ditzhuijzen NS, et al. Safety of optical coherence tomography in daily practice: a comparison with intravascular ultrasound. *Eur Heart J Cardiovasc Imaging*. 2017;18:467-474.
- Imola F, Mallus MT, Ramazzotti V, et al. Safety and feasibility of frequency domain optical coherence tomography to guide decision making in percutaneous coronary intervention. *EuroIntervention*. 2010;6:575-581.
- Terada N, Kuramochi T, Sugiyama T, et al. Ventricular fibrillation during optical coherence tomography/optical frequency domain imaging—a large single-center experience. *Circ J*. 2020;84:178-185.
- van der Sijde JN, Guagliumi G, Sirbu V, et al. The OPTIS Integrated System: real-time, co-registration of angiography and optical coherence tomography. *EuroIntervention*. 2016;12:855-860.
- Leistner DM, Riedel M, Steinbeck L, et al. Real-time optical coherence tomography coregistration with angiography in percutaneous coronary intervention-impact on physician decision-making: the OPTICO-integration study. *Catheter Cardiovasc Interv*. 2018;92:30-37.
- Gerbaud E, Weisz G, Tanaka A, et al. Multi-laboratory inter-institute reproducibility study of IVOCT and IVUS assessments using published consensus document definitions. *Eur Heart J Cardiovasc Imaging*. 2016;17:756-764.
- Ughi GJ, Van Dyck CJ, Adriaenssens T, et al. Automatic assessment of stent neointimal coverage by intravascular optical coherence tomography. *Eur Heart J Cardiovasc Imaging*. 2014;15:195-200.
- Shameer K, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? *Heart*. 2018;104:1156-1164.
- Fedewa R, Puri R, Fleischman E, et al. Artificial intelligence in intracoronary imaging. *Curr Cardiol Rep*. 2020;22:46.
- Min HS, Yoo JH, Kang SJ, et al. Detection of optical coherence tomography-defined thin-cap fibroatheroma in the coronary artery using deep learning. *EuroIntervention*. 2020;16:404-412.
- Saia F, Komukai K, Capodanno D, et al. Eroded versus ruptured plaques at the culprit site of STEMI: in vivo pathophysiological features and response to primary PCI. *JACC Cardiovasc Imaging*. 2015;8:566-575.
- Lu H, Lee J, Ray S, et al. Automated stent coverage analysis in intravascular OCT (IVOCT) image volumes using a support vector machine and mesh growing. *Biomed Opt Express*. 2019;10:2809-2828.
- Tearney GJ, Regar E, Akasaka T, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol*. 2012;59:1058-1072.
- Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary intima-media thickness by optical coherence tomography: comparison with intravascular ultrasound. *Circ J*. 2005;69:903-907.
- Jang IK, Bouma BE, Kang DH, et al. Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: comparison with intravascular ultrasound. *J Am Coll Cardiol*. 2002;39:604-609.
- Uemura S, Ishigami K, Soeda T, et al. Thin-cap fibroatheroma and micro-channel findings in optical coherence tomography correlate with subsequent progression of coronary atheromatous plaques. *Eur Heart J*. 2012;33:78-85.
- Yabushita H, Bouma BE, Houser SL, et al. Characterization of human atherosclerosis by optical coherence tomography. *Circulation*. 2002;106:1640-1645.
- Kawasaki M, Bouma BE, Bressner J, et al. Diagnostic accuracy of optical coherence tomography and integrated backscatter intravascular ultrasound images for tissue characterization of human coronary plaques. *J Am Coll Cardiol*. 2006;48:81-88.
- Yonetsu T, Kakuta T, Lee T, et al. In vivo critical fibrous cap thickness for rupture-prone coronary plaques assessed by optical coherence tomography. *Eur Heart J*. 2011;32:1251-1259.
- Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary arterial plaque by optical coherence tomography. *Am J Cardiol*. 2006;97:1172-1175.
- Manfrini O, Mont E, Leone O, et al. Sources of error and interpretation of plaque morphology by optical coherence tomography. *Am J Cardiol*. 2006;98:156-159.
- Stamper D, Weissman NJ, Brezinski M. Plaque characterization with optical coherence tomography. *J Am Coll Cardiol*. 2006;47:C69-C79.
- Sluiter JC, Kolodgie FD, Bijnens AP, et al. Thin-walled microvessels in human coronary atherosclerotic plaques show incomplete endothelial junctions relevance of compromised structural integrity for intraplaque microvascular leakage. *J Am Coll Cardiol*. 2009;53:1517-1527.
- Galon MZ, Wang Z, Bezerra HG, et al. Differences determined by optical coherence tomography volumetric analysis in non-culprit lesion morphology and inflammation in ST-segment elevation myocardial infarction and stable angina pectoris patients. *Catheter Cardiovasc Interv*. 2015;85:E108-E115.
- MacNeill BD, Jang IK, Bouma BE, et al. Focal and multi-focal plaque macrophage distributions in patients with acute and stable presentations of coronary artery disease. *J Am Coll Cardiol*. 2004;44:972-979.
- Raffel OC, Tearney GJ, Gauthier DD, Halpern EF, Bouma BE, Jang IK. Relationship between a systemic inflammatory marker, plaque inflammation, and plaque characteristics determined by intravascular optical coherence tomography. *Arterioscler Thromb Vasc Biol*. 2007;27:1820-1827.
- Katayama Y, Tanaka A, Taruya A, et al. Feasibility and clinical significance of in vivo cholesterol crystal detection using optical coherence tomography. *Arterioscler Thromb Vasc Biol*. 2020;40:220-229.
- Slager CJ, Wentzel JJ, Gijzen FJ, et al. The role of shear stress in the destabilization of vulnerable plaques and related therapeutic implications. *Nat Clin Pract Cardiovasc Med*. 2005;2:456-464.
- Vanzetto G, Berger-Coiz E, Barone-Rochette G, et al. Prevalence, therapeutic management and medium-term prognosis of spontaneous coronary artery dissection: results from a database of 11,605 patients. *Eur J Cardiothorac Surg*. 2009;35:250-254.
- Alfonso F, Paulo M, Gonzalo N, et al. Diagnosis of spontaneous coronary artery dissection by optical coherence tomography. *J Am Coll Cardiol*. 2012;59:1073-1039.
- Poon K, Bell B, Raffel OC, Walters DL, Jang IK. Spontaneous coronary artery dissection: utility of intravascular ultrasound and optical coherence tomography during percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2011;4:e5-e7.
- Johnson TW, Räber L, Di Mario C, et al. Clinical use of intracoronary imaging. Part 2: acute coronary syndromes, ambiguous coronary angiography findings, and guiding interventional decision-making: an expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *EuroIntervention*. 2019;15:434-451.
- Shin ES, Ann SH, Singh GB, et al. OCT-defined morphological characteristics of coronary artery spasm sites in vasospastic angina. *JACC Cardiovasc Imaging*. 2015;8:1059-1067.
- Muller JE, Toffler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation*. 1989;79:733-743.
- Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol*. 2005;46:937-954.
- Slager CJ, Wentzel JJ, Gijzen FJ, et al. The role of shear stress in the generation of rupture-prone vulnerable plaques. *Nat Clin Pract Cardiovasc Med*. 2005;2:401-407.
- Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part II. *Circulation*. 2003;108:1772-1778.
- Wang JC, Normand SL, Mauri L, Kuntz RE. Coronary artery spatial distribution of acute myocardial infarction occlusions. *Circulation*. 2004;110:278-284.
- Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med*. 1997;336:1276-1282.
- Tatebe S, Fukumoto Y, Sugimura K, et al. Optical coherence tomography is superior to intravascular ultrasound for diagnosis of distal-type chronic thromboembolic pulmonary hypertension. *Circ J*. 2013;77:1081-1083.
- Meissner OA, Rieber J, Babaryka G, et al. Intravascular optical coherence tomography: comparison with histopathology in atherosclerotic peripheral artery specimens. *J Vasc Interv Radiol*. 2006;17:343-349.
- Brown AJ, Obaid DR, Costopoulos C, et al. Direct comparison of virtual-histology intravascular ultrasound and optical coherence tomography imaging for identification of thin-cap fibroatheroma. *Circ Cardiovasc Imaging*. 2015;8:e003487.
- Fujii K, Hao H, Shibuya M, et al. Accuracy of OCT, grayscale IVUS, and their combination for the diagnosis of coronary TCFA: an ex vivo validation study. *JACC Cardiovasc Imaging*. 2015;8:451-460.
- Nakano M, Yahagi K, Yamamoto H, et al. Additive value of integrated backscatter IVUS for detection of vulnerable plaque by optical frequency domain imaging: an ex vivo autopsy study of human coronary arteries. *JACC Cardiovasc Imaging*. 2016;9:163-172.
- Phipps JE, Hoyt T, Vela D, et al. Diagnosis of Thin-capped fibroatheromas in intravascular optical coherence tomography images: effects of light scattering. *Circ Cardiovasc Interv*. 2016;9.
- Suzuki N, Guagliumi G, Bezerra HG, et al. The impact of an eccentric intravascular ImageWire during coronary optical coherence tomography imaging. *EuroIntervention*. 2011;6:963-969.
- Mann J, Davies MJ. Mechanisms of progression in native coronary artery disease: role of healed plaque disruption. *Heart*. 1999;82:265-268.
- Burke AP, Kolodgie FD, Farb A, et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation*. 2001;103:934-940.



57. Vergallo R, Crea F. Atherosclerotic plaque healing. *N Engl J Med*. 2020;383:846-857.
58. Wang C, Hu S, Wu J, et al. Characteristics and significance of healed plaques in patients with acute coronary syndrome and stable angina: an in vivo OCT and IVUS study. *EuroIntervention*. 2019;15:e771-e778.
59. Dai J, Fang C, Zhang S, et al. Frequency, predictors, distribution, and morphological characteristics of layered culprit and nonculprit plaques of patients with acute myocardial infarction: in vivo 3-vessel optical coherence tomography study. *Circ Cardiovasc Interv*. 2020;13:e009125.
60. Fracassi F, Crea F, Sugiyama T, et al. Healed culprit plaques in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2019;73:2253-2263.
61. Shimokado A, Matsuo Y, Kubo T, et al. In vivo optical coherence tomography imaging and histopathology of healed coronary plaques. *Atherosclerosis*. 2018;275:35-42.
62. Vergallo R, Porto I, D'Amario D, et al. Coronary atherosclerotic phenotype and plaque healing in patients with recurrent acute coronary syndromes compared with patients with long-term clinical stability: an in vivo optical coherence tomography study. *JAMA Cardiol*. 2019;4:321-329.
63. Jang IK. Plaque progression: slow linear or rapid stepwise? *Circ Cardiovasc Imaging*. 2017;10:e006964.
64. Kolodgie FD, Gold HK, Burke AP, et al. Intraplate hemorrhage and progression of coronary atheroma. *N Engl J Med*. 2003;349:2316-2325.
65. Koskinas KC, Siontis GCM, Piccolo R, et al. Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials. *Eur Heart J*. 2018;39:1172-1180.
66. Ozaki Y, Garcia-Garcia HM, Beyene SS, et al. Effect of statin therapy on fibrous cap thickness in coronary plaque on optical coherence tomography—review and meta-analysis. *Circ J*. 2019;83:1480-1488.
67. Räber L, Koskinas KC, Yamaji K, et al. Changes in Coronary plaque composition in patients with acute myocardial infarction treated with high-intensity statin therapy (IBIS-4): a serial optical coherence tomography study. *JACC Cardiovasc Imaging*. 2019;12:1518-1528.
68. Jia H, Abtahian F, Aguirre AD, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol*. 2013;62:1748-1758.
69. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol*. 2006;47:C13-C18.
70. Higuma T, Soeda T, Abe N, et al. A combined optical coherence tomography and intravascular ultrasound study on plaque rupture, plaque erosion, and calcified nodule in patients with ST-segment elevation myocardial infarction: incidence, morphologic characteristics, and outcomes after percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2015;8:1166-1176.
71. Lee T, Mintz GS, Matsumura M, et al. Prevalence, predictors, and clinical presentation of a calcified nodule as assessed by optical coherence tomography. *JACC Cardiovasc Imaging*. 2017;10:883-891.
72. Alfonso F, Prati F. Optical coherence tomography to predict plaque progression: a glimpse into the crystal ball? *JACC Cardiovasc Imaging*. 2021;14:1639-1643.
73. Schaar JA, Muller JE, Falk E, et al. Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. *Eur Heart J*. 2004;25:1077-1082.
74. Dai J, Xing L, Jia H, et al. In vivo predictors of plaque erosion in patients with ST-segment elevation myocardial infarction: a clinical, angiographical, and intravascular optical coherence tomography study. *Eur Heart J*. 2018;39:2077-2085.
75. Niccoli G, Montone RA, Di Vito L, et al. Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome. *Eur Heart J*. 2015;36:1377-1384.
76. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20:1262-1275.
77. Jia H, Dai J, Hou J, et al. Effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based management in plaque erosion (the EROSION study). *Eur Heart J*. 2017;38:792-800.
78. Prati F, Uemura S, Souteyrand G, et al. OCT-based diagnosis and management of STEMI associated with intact fibrous cap. *JACC Cardiovasc Imaging*. 2013;6:283-287.
79. Xing L, Yamamoto E, Sugiyama T, et al. EROSION study (Effective Anti-Thrombotic Therapy Without Stenting: intravascular optical coherence tomography-based management in plaque erosion): a 1-year follow-up report. *Circ Cardiovasc Interv*. 2017;10:e005860.
80. Sugiyama T, Yamamoto E, Fracassi F, et al. Calcified plaques in patients with acute coronary syndromes. *JACC Cardiovasc Interv*. 2019;12:531-540.
81. Escaned J, Ryan N, Mejia-Renteria H, et al. Safety of the deferral of coronary revascularization on the basis of instantaneous wave-free ratio and fractional flow reserve measurements in stable coronary artery disease and acute coronary syndromes. *JACC Cardiovasc Interv*. 2018;11:1437-1449.
82. Hakeem A, Edupuganti MM, Almomani A, et al. Long-term prognosis of deferred acute coronary syndrome lesions based on nonischemic fractional flow reserve. *J Am Coll Cardiol*. 2016;68:1181-1191.
83. Montone RA, Niccoli G, Crea F, Jang IK. Management of non-culprit coronary plaques in patients with acute coronary syndrome. *Eur Heart J*. 2020;41:3579-3586.
84. Pinilla-Echeverri N, Mehta SR, Wang J, et al. Nonculprit lesion plaque morphology in patients with ST-segment-elevation myocardial infarction: results from the COMPLETE trial optical coherence tomography sub-study. *Circ Cardiovasc Interv*. 2020;13:e008768.
85. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119-177.
86. Gerbaud E, Arabucki F, Nivet H, et al. OCT and CMR for the diagnosis of patients presenting with MINOCA and suspected epicardial causes. *JACC Cardiovasc Imaging*. 2020;13:2619-2631.
87. Reynolds HR, Maehara A, Kwong RY, et al. Coronary optical coherence tomography and cardiac magnetic resonance imaging to determine underlying causes of myocardial infarction with nonobstructive coronary arteries in women. *Circulation*. 2021;143:624-640.
88. Kerenky RA, Wade M, Deedwania P, Boden WE, Pepine CJ, Investigators VAN-Q-WISI-HVT. Revisiting the culprit lesion in non-Q-wave myocardial infarction. Results from the VANQWISH trial angiographic core laboratory. *J Am Coll Cardiol*. 2002;39:1456-1463.
89. Bezerra HG, Attizzani GF, Sirbu V, et al. Optical coherence tomography versus intravascular ultrasound to evaluate coronary artery disease and percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2013;6:228-236.
90. Kubo T, Akasaka T, Shite J, et al. OCT compared with IVUS in a coronary lesion assessment: the OPUS-CLASS study. *JACC Cardiovasc Imaging*. 2013;6:1095-1104.
91. Gonzalo N, Escaned J, Alfonso F, et al. Morphometric assessment of coronary stenosis relevance with optical coherence tomography: a comparison with fractional flow reserve and intravascular ultrasound. *J Am Coll Cardiol*. 2012;59:1080-1089.
92. Maehara A, Ben-Yehuda O, Ali Z, et al. Comparison of stent expansion guided by optical coherence tomography versus intravascular ultrasound: the ILUMIEN II Study (Observational Study of Optical Coherence Tomography [OCT] in Patients Undergoing Fractional Flow Reserve [FFR] and Percutaneous Coronary Intervention). *JACC Cardiovasc Interv*. 2015;8:1704-1714.
93. Kubo T, Shinke T, Okamura T, et al. Optical frequency domain imaging vs. intravascular ultrasound in percutaneous coronary intervention (OPINION trial): one-year angiographic and clinical results. *Eur Heart J*. 2017;38:3139-3147.
94. Ali ZA, Maehara A, Généreux P, et al. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. *Lancet*. 2016;388:2618-2628.
95. Ali Z, Landmesser U, Karimi Galoughi K, et al. Optical coherence tomography-guided coronary stent implantation compared to angiography: a multicentre randomised trial in PCI - design and rationale of ILUMIEN IV: OPTIMAL PCI. *EuroIntervention*. 2021;16:1092-1099.
96. Prati F, Guagliumi G, Mintz GS, et al. Expert review document part 2: methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. *Eur Heart J*. 2012;33:2513-2520.
97. Kini AS, Motoyama S, Vengrenyuk Y, et al. Multimodality intravascular imaging to predict periprocedural myocardial infarction during percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2015;8:937-945.
98. Lee T, Yonetsu T, Koura K, et al. Impact of coronary plaque morphology assessed by optical coherence tomography on cardiac troponin elevation in patients with elective stent implantation. *Circ Cardiovasc Interv*. 2011;4:378-386.
99. Imola F, Occhipinti M, Biondi-Zoccai G, et al. Association between proximal stent edge positioning on atherosclerotic plaques containing lipid pools and postprocedural myocardial infarction (from the CLI-POOL Study). *Am J Cardiol*. 2013;111:526-531.
100. Ino Y, Kubo T, Matsuo Y, et al. Optical coherence tomography predictors for edge restenosis after everolimus-eluting stent implantation. *Circ Cardiovasc Interv*. 2016;9:e004231.
101. Ali ZA, Nef H, Escaned J, et al. Safety and effectiveness of coronary intravascular lithotripsy for treatment of severely calcified coronary stenoses: the Disrupt CAD II study. *Circ Cardiovasc Interv*. 2019;12:e008434.
102. Hill JM, Kereiakes DJ, Shlofmitz RA, et al. Intravascular lithotripsy for treatment of severely calcified coronary artery disease. *J Am Coll Cardiol*. 2020;76:2635-2646.
103. Saito S, Yamazaki S, Takahashi A, et al. Intravascular lithotripsy for vessel preparation in severely calcified coronary arteries prior to stent placement—primary outcomes from the Japanese Disrupt CAD IV Study. *Circ J*. 2021;85:826-833.
104. Okamura T, Nagoshi R, Fujimura T, et al. Impact of guidewire recrossing point into stent jailed side branch for optimal kissing balloon dilatation: core lab 3D optical coherence tomography analysis. *EuroIntervention*. 2018;13:e1785-e1793.
105. Nagoshi R, Okamura T, Murasato Y, et al. Feasibility and usefulness of three-dimensional optical coherence tomography guidance for optimal side branch treatment in coronary bifurcation stenting. *Int J Cardiol*. 2018;250:270-274.
106. Okamura T, Onuma Y, Yamada J, et al. 3D optical coherence tomography: new insights into the process of optimal rewiring of side branches during bifurcational stenting. *EuroIntervention*. 2014;10:907-915.

107. Miyazaki Y, Muramatsu T, Asano T, et al. Online three-dimensional OFDI-guided versus angiography-guided PCI in bifurcation lesions: design and rationale of the randomised OPTIMUM trial. *EuroIntervention*. 2021;16:1333-1341.
108. Holm NR, Adriaenssens T, Motreff P, Shinke T, Dijkstra J, Christiansen EH. OCT for bifurcation stenting: what have we learned? *EuroIntervention*. 2015;11(suppl V):V64-V70.
109. Holm NR, Andreasen LN, Walsh S, et al. Rationale and design of the European randomized Optical Coherence Tomography Optimized Bifurcation Event Reduction Trial (OCTOBER). *Am Heart J*. 2018;205:97-109.
110. Mintz GS, Lefèvre T, Lassen JF, et al. Intravascular ultrasound in the evaluation and treatment of left main coronary artery disease: a consensus statement from the European Bifurcation Club. *EuroIntervention*. 2018;14:e467-e474.
111. Fujino Y, Bezerra HG, Attizzani GF, et al. Frequency-domain optical coherence tomography assessment of unprotected left main coronary artery disease—a comparison with intravascular ultrasound. *Catheter Cardiovasc Interv*. 2013;82:E173-E183.
112. Burzotta F, Dato I, Trani C, et al. Frequency domain optical coherence tomography to assess non-ostial left main coronary artery. *EuroIntervention*. 2015;10:e1-e8.
113. Amabile N, Rangé G, Souteyrand G, et al. Optical coherence tomography to guide percutaneous coronary intervention of the left main coronary artery: the LEMON study. *EuroIntervention*. 2021;17:e124-e131.
114. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
115. Hong SJ, Kim BK, Shin DH, et al. Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JAMA*. 2015;314:2155-2163.
116. Elgendy IY, Mahmoud AN, Elgendy AY, Bavry AA. Outcomes with intravascular ultrasound-guided stent implantation: a meta-analysis of randomized trials in the era of drug-eluting stents. *Circ Cardiovasc Interv*. 2016;9:e003700.
117. Zhang YJ, Pang S, Chen XY, et al. Comparison of intravascular ultrasound guided versus angiography guided drug eluting stent implantation: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2015;15:153.
118. Prati F, Di Vito L, Biondi-Zoccai G, et al. Angiography alone versus angiography plus optical coherence tomography to guide decision-making during percutaneous coronary intervention: the Centro per la Lotta contro l'Infarto-Optimisation of Percutaneous Coronary Intervention (CLI-OPCI) study. *EuroIntervention*. 2012;8:823-829.
119. Meneveau N, Souteyrand G, Motreff P, et al. Optical coherence tomography to optimize results of percutaneous coronary intervention in patients with non-ST-elevation acute coronary syndrome: results of the multicenter, randomized DOCTORS study (Does Optical Coherence Tomography Optimize Results of Stenting). *Circulation*. 2016;134:906-917.
120. Kang DY, Ahn JM, Park H, et al. Comparison of optical coherence tomography-guided versus intravascular ultrasound-guided percutaneous coronary intervention: rationale and design of a randomized, controlled OCTIVUS trial. *Am Heart J*. 2020;228:72-80.
121. Kubo T, Shinke T, Okamura T, et al. Comparison between optical coherence tomography guidance and angiography guidance in percutaneous coronary intervention (COCO): study protocol for a randomized controlled trial. *J Cardiol*. 2018;72:170-175.
122. Choi SY, Maehara A, Cristea E, et al. Usefulness of minimum stent cross sectional area as a predictor of angiographic restenosis after primary percutaneous coronary intervention in acute myocardial infarction (from the HORIZONS-AMI Trial IVUS substudy). *Am J Cardiol*. 2012;109:455-460.
123. Fujii K, Carlier SG, Mintz GS, et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol*. 2005;45:995-998.
124. Soeda T, Uemura S, Park SJ, et al. Incidence and clinical significance of poststent optical coherence tomography findings: one-year follow-up study from a multicenter registry. *Circulation*. 2015;132:1020-1029.
125. Prati F, Romagnoli E, Burzotta F, et al. Clinical impact of OCT findings during PCI: the CLI-OPCI II study. *JACC Cardiovasc Imaging*. 2015;8:1297-1305.
126. de Jaegere P, Mudra H, Figulla H, et al. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC Study). *Eur Heart J*. 1998;19:1214-1223.
127. Tanigawa J, Barlis P, Di Mario C. Intravascular optical coherence tomography: optimisation of image acquisition and quantitative assessment of stent strut apposition. *EuroIntervention*. 2007;3:128-136.
128. Choi SY, Witzendichler B, Maehara A, et al. Intravascular ultrasound findings of early stent thrombosis after primary percutaneous intervention in acute myocardial infarction: a Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) substudy. *Circ Cardiovasc Interv*. 2011;4:239-247.
129. Im E, Kim BK, Ko YG, et al. Incidences, predictors, and clinical outcomes of acute and late stent malapposition detected by optical coherence tomography after drug-eluting stent implantation. *Circ Cardiovasc Interv*. 2014;7:88-96.
130. Adriaenssens T, Joner M, Godschalk TC, et al. Optical coherence tomography findings in patients with coronary stent thrombosis: a report of the PRESTIGE Consortium (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort). *Circulation*. 2017;136:1007-1021.
131. Souteyrand G, Amabile N, Mangin L, et al. Mechanisms of stent thrombosis analysed by optical coherence tomography: insights from the national PESTO French registry. *Eur Heart J*. 2016;37:1208-1216.
132. Taniwaki M, Radu MD, Zaugg S, et al. Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. *Circulation*. 2016;133:650-660.
133. Kim BG, Kachel M, Kim JS, et al. Clinical implications of post-stent optical coherence tomographic findings: severe malapposition and cardiac events. *JACC Cardiovasc Imaging*. 2022;15(1):126-137.
134. Kobayashi N, Mintz GS, Witzendichler B, et al. Prevalence, features, and prognostic importance of edge dissection after drug-eluting stent implantation: an ADAPT-DES intravascular ultrasound substudy. *Circ Cardiovasc Interv*. 2016;9:e003553.
135. Qiu F, Mintz GS, Witzendichler B, et al. Prevalence and clinical impact of tissue protrusion after stent implantation: an ADAPT-DES intravascular ultrasound substudy. *JACC Cardiovasc Interv*. 2016;9:1499-507.
136. Bezerra HG, Costa MA, Guagliumi G, Rollins AM, Simon DI. Intracoronary optical coherence tomography: a comprehensive review clinical and research applications. *JACC Cardiovasc Interv*. 2009;2:1035-1046.
137. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation*. 2007;115:2435-2441.
138. Cook S, Wenaweser P, Togni M, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation*. 2007;115:2426-2434.
139. Sawada T, Shite J, Shinke T, et al. Very late thrombosis of sirolimus-eluting stent due to late malapposition: serial observations with optical coherence tomography. *J Cardiol*. 2008;52:290-295.
140. Ozaki Y, Okumura M, Ismail TF, et al. The fate of incomplete stent apposition with drug-eluting stents: an optical coherence tomography-based natural history study. *Eur Heart J*. 2010;31:1470-1476.
141. Guagliumi G, Sirbu V, Musumeci G, et al. Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging. *JACC Cardiovasc Interv*. 2012;5:12-20.
142. Räber L. Short DAPT duration for well-covered stents? *JACC Cardiovasc Imaging*. 2018;11:1820-1822.
143. Nakazawa G, Finn AV, Vorpahl M, Ladich ER, Kolodgie FD, Virmani R. Coronary responses and differential mechanisms of late stent thrombosis attributed to first-generation sirolimus- and paclitaxel-eluting stents. *J Am Coll Cardiol*. 2011;57:390-398.
144. Guagliumi G, Musumeci G, Sirbu V, et al. Optical coherence tomography assessment of in vivo vascular response after implantation of overlapping bare-metal and drug-eluting stents. *JACC Cardiovasc Interv*. 2010;3:531-539.
145. Moore P, Barlis P, Spiro J, et al. A randomized optical coherence tomography study of coronary stent strut coverage and luminal protrusion with rapamycin-eluting stents. *JACC Cardiovasc Interv*. 2009;2:437-444.
146. Kwon SW, Kim BK, Kim TH, et al. Qualitative assessment of neointimal tissue after drug-eluting stent implantation: comparison between follow-up optical coherence tomography and intravascular ultrasound. *Am Heart J*. 2011;161:367-372.
147. Otsuka F, Byrne RA, Yahagi K, et al. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. *Eur Heart J*. 2015;36:2147-2159.
148. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol*. 2011;57:1314-1322.
149. Yonetsu T, Kato K, Kim SJ, et al. Predictors for neoatherosclerosis: a retrospective observational study from the optical coherence tomography registry. *Circ Cardiovasc Imaging*. 2012;5:660-666.
150. Kang SJ, Mintz GS, Akasaka T, et al. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation*. 2011;123:2954-2963.
151. Takarada S, Imanishi T, Ishibashi K, et al. The effect of lipid and inflammatory profiles on the morphological changes of lipid-rich plaques in patients with non-ST-segment elevated acute coronary syndrome: follow-up study by optical coherence tomography and intravascular ultrasound. *JACC Cardiovasc Interv*. 2010;3:766-772.
152. Takano M, Yamamoto M, Inami S, et al. Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents extended late-phase observation by intracoronary optical coherence tomography. *J Am Coll Cardiol*. 2009;55:26-32.
153. Yonetsu T, Kim JS, Kato K, et al. Comparison of incidence and time course of neoatherosclerosis between bare metal stents and drug-eluting stents using optical coherence tomography. *Am J Cardiol*. 2012;110:933-939.
154. Vergallo R, Yonetsu T, Uemura S, et al. Correlation between degree of neointimal hyperplasia and incidence and characteristics of neoatherosclerosis as assessed by optical coherence tomography. *Am J Cardiol*. 2013;112:1315-1321.
155. Hou J, Qi H, Zhang M, et al. Development of lipid-rich plaque inside bare metal stent: possible mechanism of late stent thrombosis? An optical coherence tomography study. *Heart*. 2010;96:1187-1190.
156. Higo T, Ueda Y, Oyabu J, et al. Atherosclerotic and thrombogenic neointima formed over sirolimus drug-eluting stent: an angioscopic study. *JACC Cardiovasc Imaging*. 2009;2:616-624.
157. Nakazawa G, Vorpahl M, Finn AV, Narula J, Virmani R. One step forward and two steps back with drug-eluting-stents: from preventing restenosis to



- causing late thrombosis and nouveau atherosclerosis. *JACC Cardiovasc Imaging*. 2009;2:625-628.
158. Armstrong EJ, Feldman DN, Wang TY, et al. Clinical presentation, management, and outcomes of angiographically documented early, late, and very late stent thrombosis. *JACC Cardiovasc Interv*. 2012;5:131-140.
159. Isodono K, Fujii K, Fujimoto T, et al. The frequency and clinical characteristics of in-stent restenosis due to calcified nodule development after coronary stent implantation. *Int J Cardiovasc Imaging*. 2021;37:15-23.
160. Yin D, Mintz GS, Song L, et al. In-stent restenosis characteristics and repeat stenting underexpansion: insights from optical coherence tomography. *EuroIntervention*. 2020;16:e335-e343.
161. Hou J, Lv H, Jia H, et al. OCT assessment of allograft vasculopathy in heart transplant recipients. *JACC Cardiovasc Imaging*. 2012;5:662-663.
162. Ding D, Huang J, Westra J, et al. Immediate post-procedural functional assessment of percutaneous coronary intervention: current evidence and future directions. *Eur Heart J*. 2021;42:2695-2707.
163. Yu W, Huang J, Jia D, et al. Diagnostic accuracy of intracoronary optical coherence tomography-derived fractional flow reserve for assessment of coronary stenosis severity. *EuroIntervention*. 2019;15:189-197.
164. Tian J, Ren X, Vergallo R, et al. Distinct morphological features of ruptured culprit plaque for acute coronary events compared to those with silent rupture and thin-cap fibroatheroma: a combined optical coherence tomography and intravascular ultrasound study. *J Am Coll Cardiol*. 2014;63:2209-2216.
165. Garg S, Serruys PW, van der Ent M, et al. First use in patients of a combined near infra-red spectroscopy and intra-vascular ultrasound catheter to identify composition and structure of coronary plaque. *EuroIntervention*. 2010;5:755-756.
166. Ughi GJ, Verjans J, Fard AM, et al. Dual modality intravascular optical coherence tomography (OCT) and near-infrared fluorescence (NIRF) imaging: a fully automated algorithm for the distance-calibration of NIRF signal intensity for quantitative molecular imaging. *Int J Cardiovasc Imaging*. 2015;31:259-268.
167. Ughi GJ, Wang H, Gerbaud E, et al. Clinical characterization of coronary atherosclerosis with dual-modality OCT and near-infrared autofluorescence imaging. *JACC Cardiovasc Imaging*. 2016;9:1304-1314.
168. Liu L, Gardecki JA, Nadkarni SK, et al. Imaging the subcellular structure of human coronary atherosclerosis using micro-optical coherence tomography. *Nat Med*. 2011;17:1010-1014.
169. Yin B, Hyun C, Gardecki JA, Tearney GJ. Extended depth of focus for coherence-based cellular imaging. *Optica*. 2017;4:959-965.
170. Nishimiya K, Tearney G. Micro optical coherence tomography for coronary imaging. *Front Cardiovasc Med*. 2021;8:613400.



18 Intervention For Lower Extremity Arterial Disease

SCOTT KINLAY

CLINICAL ASSESSMENT, 337

Causes of Peripheral Artery Disease, 337

Acute Limb Ischemia, 337

Chronic Limb Ischemia, 338

Physical Examination, 339

Physiological Tests, 339

Arterial Imaging, 339

PERCUTANEOUS REVASCULARIZATION TOOLS, 340

Approach and Access, 340

Guides and Sheaths, 343

Wires, 343

Anticoagulation, 343

Reentry Devices, 345

Other Chronic Total Occlusion Devices, 346

Balloon Angioplasty, 346

Drug-Coated Balloons, 347

Stents, 347

Covered Stents, 348

Drug-Eluting Stents, 348

CONTROVERSY OVER PACLITAXEL-COATED BALLOONS AND STENTS, 349

Atherectomy, 349

Laser Atherectomy, 351

Intravascular Lithotripsy, 351

Brachytherapy, 351

Catheter-Based Thrombolysis, 351

Mechanical and Aspiration Thrombectomy, 353

Intravascular Imaging, 355

INTERVENTIONS IN SPECIFIC ARTERIES, 355

Aortoiliac Interventions, 355

Superficial Femoral Artery, 356

Popliteal Artery, 357

Tibial Arteries, 357

Venous and Prosthetic Graft

Interventions, 359

CONCLUSIONS, 360

CLINICAL ASSESSMENT

Peripheral artery disease (PAD) is caused by a number of pathologies affecting the arteries of the lower extremities. The most common cause in industrialized countries is atherosclerosis, but interventionalists need to be aware of other pathologies that may be best treated by noninterventional approaches. The history and physical examination can distinguish most causes of PAD and determine the need for further testing and the urgency of interventional therapy.

Causes of Peripheral Artery Disease

Atherosclerosis is the most common cause of PAD, principally related to the conventional risk factors of age, cigarette smoking, elevated cholesterol level, hypertension, diabetes mellitus, and associated inactivity and obesity.^{1,2} Other causes of arterial disease include aneurysms, dissections, emboli, compression syndromes, and vasculitis.

About 50% to 90% of patients with atherosclerotic PAD are asymptomatic.^{1,2} The diagnosis is made by clinical examination or other tests that are clinically indicated or ordered for other reasons. Asymptomatic disease is a marker of elevated risk of cardiovascular events but usually does not require revascularization.^{1,2} Thus, the interventionalist shares responsibility in starting risk factor modification by encouraging smoking cessation, initiating treatment for hyperlipidemia and hypertension, and promoting physical activity.

The symptoms of PAD help distinguish acute from chronic presentations and often give an indication of the

location of disease. The temporal relationship of disease onset is particularly important in determining the urgency of treatment.

Acute Limb Ischemia

Acute limb ischemia (ALI) is a sudden decrease in perfusion (defined as within 14 days) that threatens the viability of the limb. Rapid assessment and treatment are needed to salvage the limb, although a high mortality often relates to coexisting comorbidities.¹⁻³ ALI is caused by embolization most commonly from the heart; in situ thrombosis related to atherosclerosis (Figure 18.1); or increasingly, graft thrombosis or stent thrombosis.

Emboli may occur in patients without symptoms or signs of preceding PAD. In situ thrombosis is often accompanied by signs of atherosclerosis in both limbs, but it can occur from impaired flow in a graft or stent (e.g., restenosis or graft hyperplasia), thrombosis of a popliteal aneurysm, hypercoagulable states, or dissection.

The classic symptoms and signs of ALI are known as the *six Ps*. These are pain, pallor, pulseless, poikilothermia (a cold limb), paresthesia, and paralysis. The order of these symptoms and signs also relates to the viability of the limb and whether revascularization will salvage it.¹⁻³

As sensory and motor function is lost progressively from the distal to proximal limb, a simple test of intact motor function is dorsiflexion of the big toe to resistance. Table 18.1 shows the Rutherford classification¹⁻³ of ALI and the management. Patients with Rutherford class I and IIa may be able to tolerate an overnight infusion of catheter-based thrombolysis. Patients with class IIb

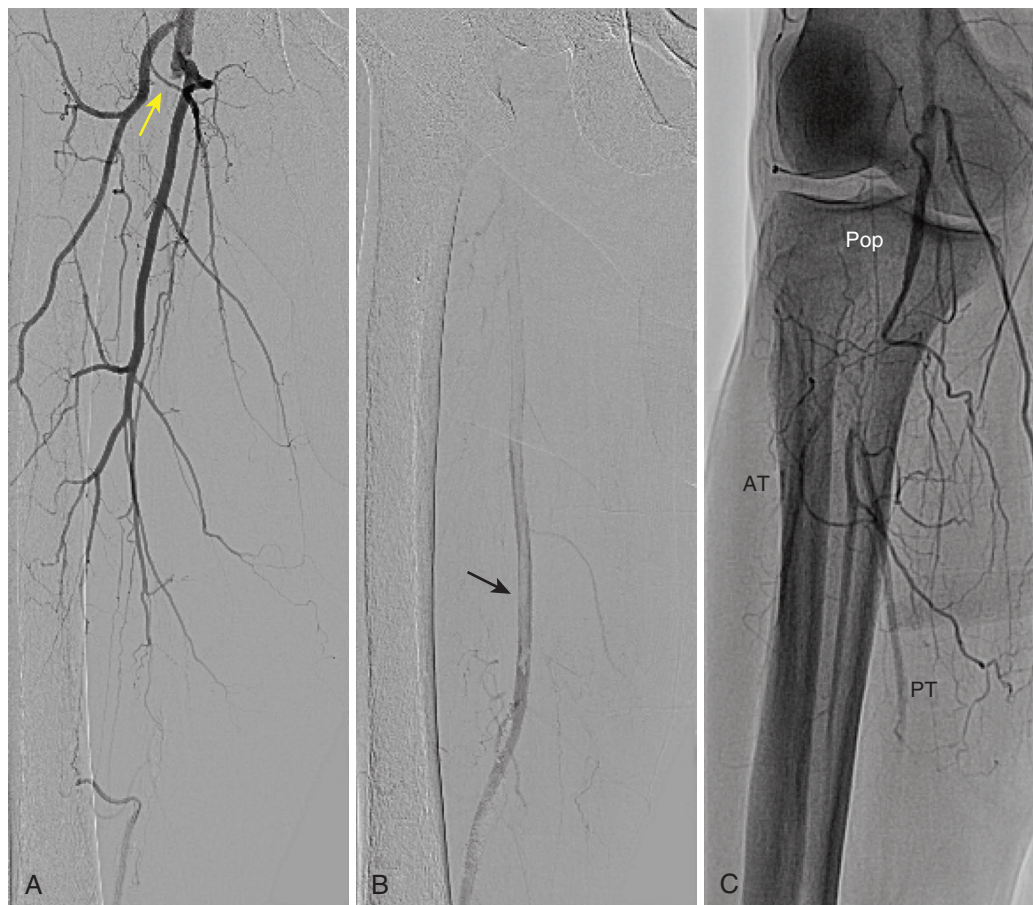


FIGURE 18.1 Angiograms from a 73-year-old man with multiple comorbidities and acute limb ischemia. **A**, An occluded right superficial femoral artery (arrow) and patent profunda artery in the early phase of the angiogram. **B**, Late phase of the angiogram showing a long filling defect in the superficial femoral artery consistent with in situ thrombus (arrow). **C**, Occlusion of the distal popliteal artery, peroneal tibial trunk, and proximal anterior tibial artery (AT) from embolized thrombus. *Pop*, Popliteal artery; *PT*, posterior tibial.

TABLE 18.1 Rutherford Classification of Acute Limb Ischemia

RUTHERFORD CLASS	PROGNOSIS	SENSORY EXAM	MOTOR EXAM	ARTERIAL DOPPLER SIGNAL	VENOUS DOPPLER SIGNAL	SKIN EXAM	INITIAL THERAPY	DEFINITIVE THERAPY
Class I viable, not threatened	Not immediately threatened	Normal	Normal	Audible	Audible	Normal capillary return	Anticoagulation	Imaging and urgent revascularization
Class IIa: marginally threatened	Salvageable with prompt therapy	Minimal loss	Normal	Often inaudible	Audible	Decreased capillary return	Anticoagulation	Imaging and emergency revascularization
Class IIb: immediately threatened	Salvageable if treated immediately	Mild sensory loss and rest pain	Mildly to moderately abnormal	Usually inaudible	Audible	Pallor	Anticoagulation	+/- Imaging and emergency revascularization
Class III: irreversible	Irreversible tissue and nerve damage	Profound loss	Paralysis and rigor	Inaudible	Inaudible	No capillary return and marbling	Anticoagulation	Amputation

Adapted from Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg.* 2007;45(suppl S):S5-S67 and Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg.* 1997;26:517-538.

ischemia require more immediate revascularization by endovascular aspiration or mechanical thrombectomy in conjunction with thrombolysis^{1,2,4,5} or classically by surgical embolectomy or bypass grafting. Typically, surgical treatment is used if fasciotomy is required to prevent or treat a compartment syndrome associated with reperfusion injury and edema of the revascularized limb.

Chronic Limb Ischemia

Chronic limb ischemia has an indolent presentation and is far more common than ALI. The two classifications of chronic limb ischemia are the Rutherford scale commonly used in the United States and the Fontaine scale commonly used in Europe (Table 18.2).^{1,2,6} Both scales distinguish the two main clinical presentations of intermittent

TABLE 18.2 Rutherford Categories and Fontaine Stages of Chronic Limb Ischemia in Peripheral Artery Disease⁷

PAD CLASSIFICATION	CLINICAL SYMPTOM	RUTHERFORD	FONTAINE
Asymptomatic	Asymptomatic	0	I
Intermittent claudication	Mild claudication	1	IIa
	Moderate claudication	2	IIb
	Severe claudication	3	IIb
Chronic limb threatening ischemia or critical limb ischemia	Ischemic rest pain	4	III
	Minor tissue loss	5	IV
	Ulceration or gangrene	6	IV

PAD, Peripheral artery disease.

claudication and critical limb ischemia (CLI or chronic limb-threatening ischemia).

Intermittent claudication is classically described as a cramping, aching discomfort or pain with exercise that is relieved by rest. Claudication results from muscle ischemia caused by an inability to augment blood flow to a leg muscle related to a stenosis or occlusion of the large or small arteries (or both). However, up to half of symptomatic patients describe atypical symptoms with exercise, including fatigue, slow walking speed, and gait disturbance.⁸ Claudication has major effects on quality of life by impairing function and activity. It also relates to a high risk of cardiovascular events over the subsequent years. The risk of limb loss is usually low, so it is perfectly safe and appropriate to attempt medical therapies (e.g., exercise programs, cilostazol) for several months before considering revascularization. In many cases, medical therapy resolves symptoms and improves quality of life and function to a level at which revascularization is unlikely to offer extra benefits.

Chronic limb threatening ischemia (CLTI) also known as critical limb ischemia (CLI) occurs when blood flow at rest is inadequate to meet metabolic demands. Symptoms include pain at rest usually in the lower leg and often with a sensation of coldness or numbness in the limb. Symptoms are exacerbated by cold and leg elevation and relieved by leg dependency (e.g., hanging the leg over the edge of the bed) to improve blood flow to the foot by gravity. Ischemia can progress to infarction with gangrene and ulceration. Patients with CLTI/CLI are at high risk of major amputation (amputation above the ankle), myocardial infarction, and stroke.^{1,2,6} Thus, the goals of therapy are to improve blood flow through revascularization and ensure adequate treatment of risk factors for atherosclerosis.

Physical Examination

The examination should include a complete check of the skin, heart, lungs, abdomen, and upper and lower limbs to look for systemic disease and causes of lower limb ischemia.⁶ A blood pressure difference of more than 15 to 20 mm Hg between each arm indicates significant unilateral upper extremity disease. All peripheral pulses are palpated and coded as absent or present.^{1,2} Diminished pulses may be reported, but this is a less reproducible classification. Expansile or hyperdynamic pulses may indicate aneurysms (e.g., of the abdominal aorta or popliteal artery). Auscultation of bruits indicates disturbed or

turbulent flow and may indicate a stenosis. Shoes and socks should be removed to look for ulceration or gangrene, which may be painless and missed by patients with neuropathy. Arterial ulcers often have a dry base or an overlying eschar, in contrast to venous ulcers, which are beefier and moister. More severe forms of ischemia lead to pallor and coolness of the limb, particularly on elevation, and in CLTI/CLI, lowering the limb will reveal a dependent rubor caused by hyperemia related to arteriolar and venule dilation and improved flow with gravity.

Physiological Tests

The ankle brachial index (ABI) is a simple office-based method to identify PAD. A handheld 5- to 10-MHz Doppler device is used in conjunction with a conventional blood pressure cuff to measure the systolic pressure at both brachial arteries and the pedal arteries in both feet. Recent guidelines recommend recording the ABI for each limb as the highest pedal pressure in that limb over the highest brachial artery pressure.^{1,2} A normal ABI is greater than 1.0 up to 1.4. Higher ABIs often indicate calcification of the tibial arteries, in which case the ABI is unreliable for identifying obstructive disease. An ABI of 0.9 to 1.0 is borderline, and an ABI of less than 0.9 is abnormal and a sensitive and specific indicator of obstructive PAD as well as elevated risk of cardiovascular events.

Vascular laboratories are able to provide additional physiological data beyond the ABI.^{1,2,7} These include segmental leg pressures that help to localize disease by using blood pressure cuffs at different locations to identify marked drops in systolic pressure between cuffs. Pulse volume recordings use blood pressure cuffs expanded to low pressure and identify the subtle expansion of the limb with each systole. These are particularly useful when calcified arteries prevent accurate measurements of ABI. Treadmill testing using standardized walking protocols can quantify the walking times or distances and identify a decrease in ankle pressure with exercise in patients with PAD who have borderline results at rest.^{7,9}

Arterial Imaging

Duplex ultrasonography uses a combination of B-mode two-dimensional grayscale imaging with color-encoded Doppler imaging and pulsed-Doppler velocity analysis.^{1,2,10} Grayscale imaging and color Doppler can identify the



artery and direction of blood flow, but they are not reliable at grading the degree of stenosis. Stenoses are identified by turbulent flow with varying velocities and graded by pulsed-Doppler comparing velocities in the stenosed segment to a proximal reference segment. Greater stenosis relates to increasing peak and subsequently diastolic flow velocities.

Magnetic resonance angiography uses two techniques to identify arteries by coding blood flow white (Figure 18.2). These include time-of-flight techniques and contrast-enhanced imaging. Time-of-flight relies on laminar blood flow. It tends to overestimate stenosis severity compared with conventional angiography, particularly in regions of disturbed blood flow (e.g., at bifurcations) and regions with reversal of flow. Contrast-enhanced techniques use one of several contrast agents such as gadolinium. Contrast increases the accuracy of the imaging and is better able to define smaller distal arteries. Three-dimensional (3D) rendering can allow the reader to rotate the image to help identify eccentric stenoses (see Figure 18.2). A disadvantage of gadolinium is the small risk of disabling nephrogenic systemic sclerosis, which is related to renal function and a particular concern in patients with end-stage renal disease on dialysis. For this reason, gadolinium is usually avoided in patients with severe renal dysfunction.

Computed tomographic angiography uses high-resolution x-ray scanners and iodinated contrast to image the arteries. Volume and 3D rendering can strip surrounding tissue away from the artery images and provide images similar to conventional angiography or magnetic resonance imaging. High-resolution multidetector computed tomography is generally faster than magnetic resonance angiography, but it is sometimes difficult to assess stenosis severity in heavily calcified arteries because of the

blooming effect around calcium. Most techniques require 100 mL or more of iodinated contrast, which limits its use in patients with renal dysfunction at risk of contrast nephropathy.

Invasive conventional angiography is still considered the gold standard for arterial imaging, using either digital conventional “cine” imaging or digital subtraction angiography, which removes nonarterial structures to better view the artery (see Figure 18.2). Noninvasive angiography has largely superseded the need for conventional angiography in the diagnosis and location of disease, but invasive angiography can provide additional physiological assessment of specific lesions using pressure gradients at rest and with vasodilators. Generally, a 10-mm Hg gradient at rest or a 15- to 20-mm Hg gradient with vasodilators (e.g., nitroglycerin) is considered significant. However, even a 4-Fr catheter placed through a lesion can falsely increase the gradient. Measuring gradients by pullback from proximal to distal or using 0.014-inch pressure wires helps avoid this error.

PERCUTANEOUS REVASCULARIZATION TOOLS

Approach and Access

The four major access sites for a lower limb artery are retrograde access from the contralateral femoral artery, antegrade access via the ipsilateral femoral artery, access via an upper limb radial or brachial artery traversing the aorta, and retrograde access via an ipsilateral distal artery such as the popliteal or tibial arteries (Figure 18.3). Each access has its advantages and disadvantages.

Retrograde access of the contralateral femoral artery is familiar to many interventional cardiologists, and sheath

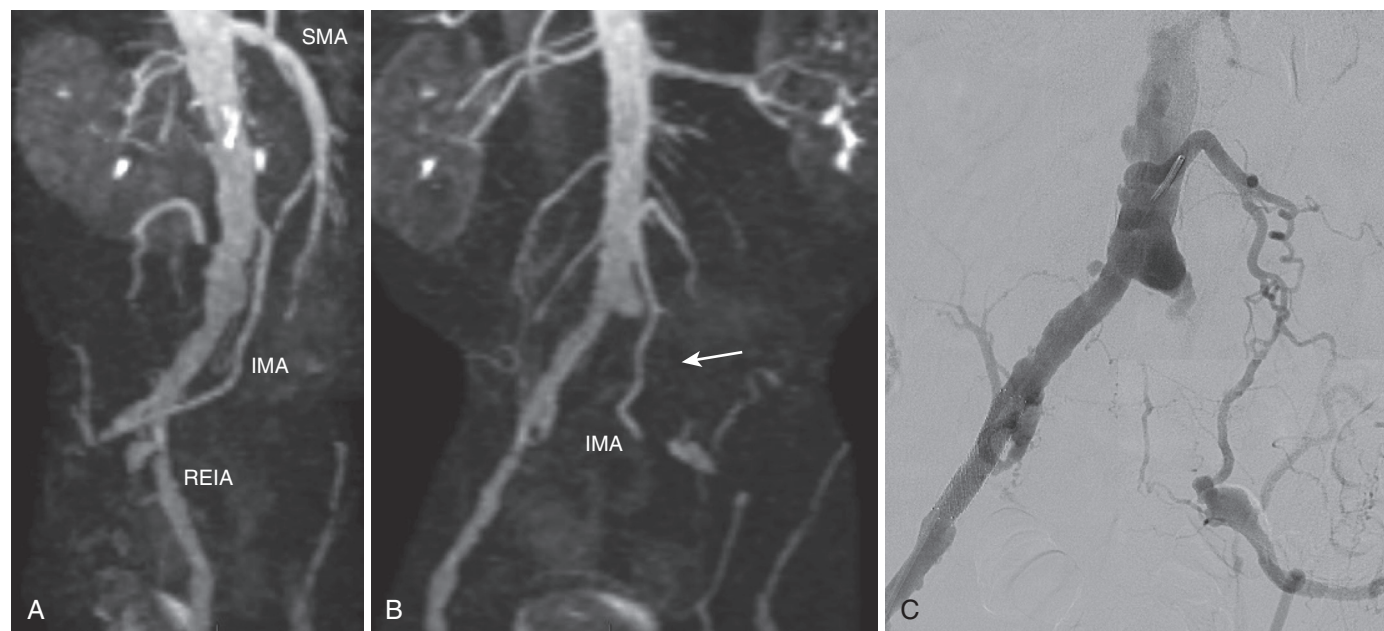


FIGURE 18.2 Comparison of magnetic resonance angiography and digital subtraction angiography (DSA). **A**, Lateral rotation of a maximum intensity image (MIP) of the lower aorta and iliac arteries. **B**, Anteroposterior rotation from an MIP showing the left common iliac occlusion (arrow) and inferior mesenteric artery (IMA) supplying collaterals to the left external iliac artery. **C**, Corresponding image from conventional angiography with DSA. REIA, Right external iliac artery; SMA, superior mesenteric artery. (From Kinlay S, Bhatt DL. Treatment of noncoronary obstructive vascular disease. In: *Braunwald Heart Disease*, ed 12. Elsevier; 2022:863.e3.)

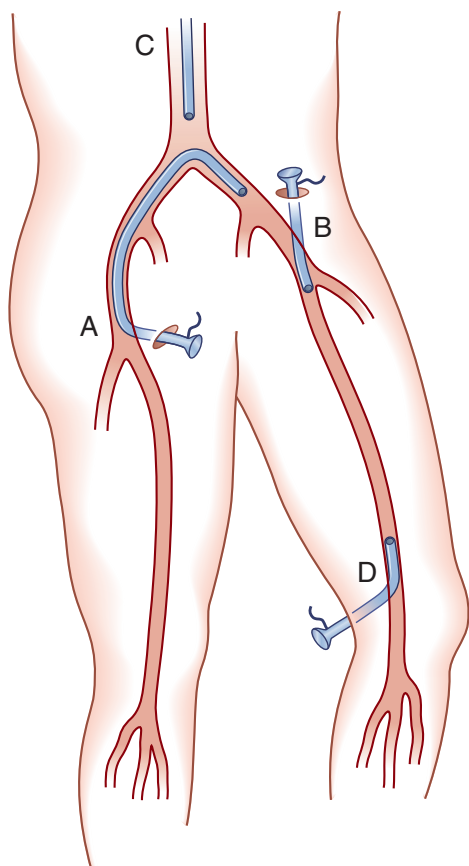


FIGURE 18.3 Potential access sites to treat peripheral artery disease. **A**, Contralateral common femoral access and up over the aortic bifurcation. **B**, Antegrade common femoral access. **C**, Radial or brachial artery access with a guide or sheath in the lower aorta. **D**, Retrograde access from a more distal artery (e.g., popliteal or pedal artery).

removal at the end of the case is facilitated by a number of closure devices (Figure 18.4). Catheters and sheaths are directed over the aortoiliac bifurcation into the contralateral leg. This provides easy access to the iliac, common femoral, and proximal superficial femoral arteries and is often used to treat more distal disease. The advantages of this approach are the ability to quickly balloon occlude the distal aorta or proximal contralateral iliac artery in the event of perforation of a more distal artery and the ability to treat the contralateral common femoral and proximal superficial femoral arteries. The disadvantages are that it may be difficult to negotiate a tortuous or calcified iliac artery system, and it may offer less support to push through extensive disease in the distal arteries (popliteal or tibial arteries).

The radial or brachial artery of the upper limb artery can provide access to the lower limbs. Traditionally, the brachial artery was used as sheath and interventional equipment were usually 100 to 130 mm in length, and this permitted access to the iliac and common femoral arteries (Figure 18.5). However, more recently, longer sheaths up to 150 cm with balloon and stent delivery devices on 200-mm shafts have permitted successful treatment from the radial artery to the level of the distal superficial femoral artery (R2P, Terumo Interventional Systems; https://www.accessdata.fda.gov/cdrh_docs/pdf19/K193125.pdf).

Antegrade access of an ipsilateral femoral artery is useful for providing greater support for popliteal and tibial interventions (see Figure 18.4D). It requires skin entry well above the common femoral artery and is therefore more difficult and often not feasible in overweight or obese patients. Because the subcutaneous path to the femoral artery is usually longer than with retrograde femoral artery

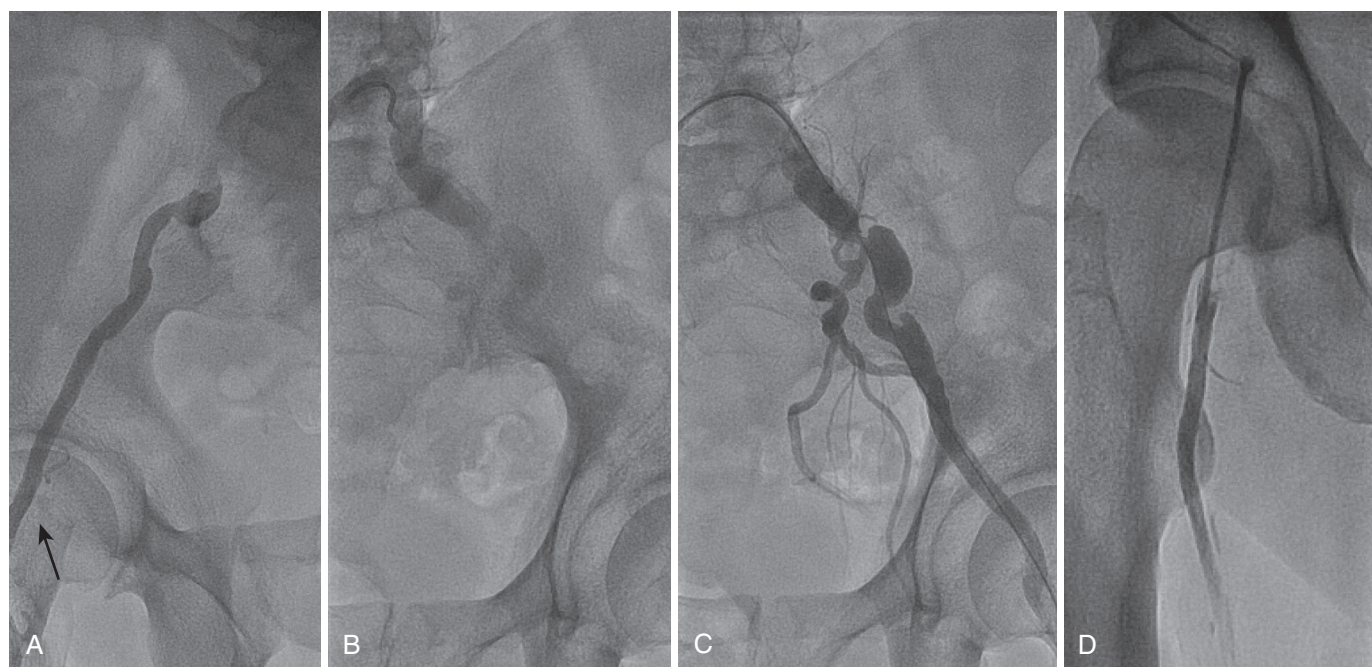


FIGURE 18.4 Access to a left iliac stenosis via the right common femoral artery. **A**, Access of the right femoral artery. Arrow indicates the tip of the femoral sheath. **B**, An Omniflush catheter is directed from the right iliac artery into the left iliac artery, and a support wire is used to direct a sheath into the left iliac artery for the intervention. **D**, Antegrade access of the common femoral artery with the sheath tip directed into the superficial femoral artery. (From Kinlay S, Bhatt DL. Treatment of noncoronary obstructive vascular disease. In: Braunwald Heart Disease, ed 12. Elsevier; 2022:864.e1).

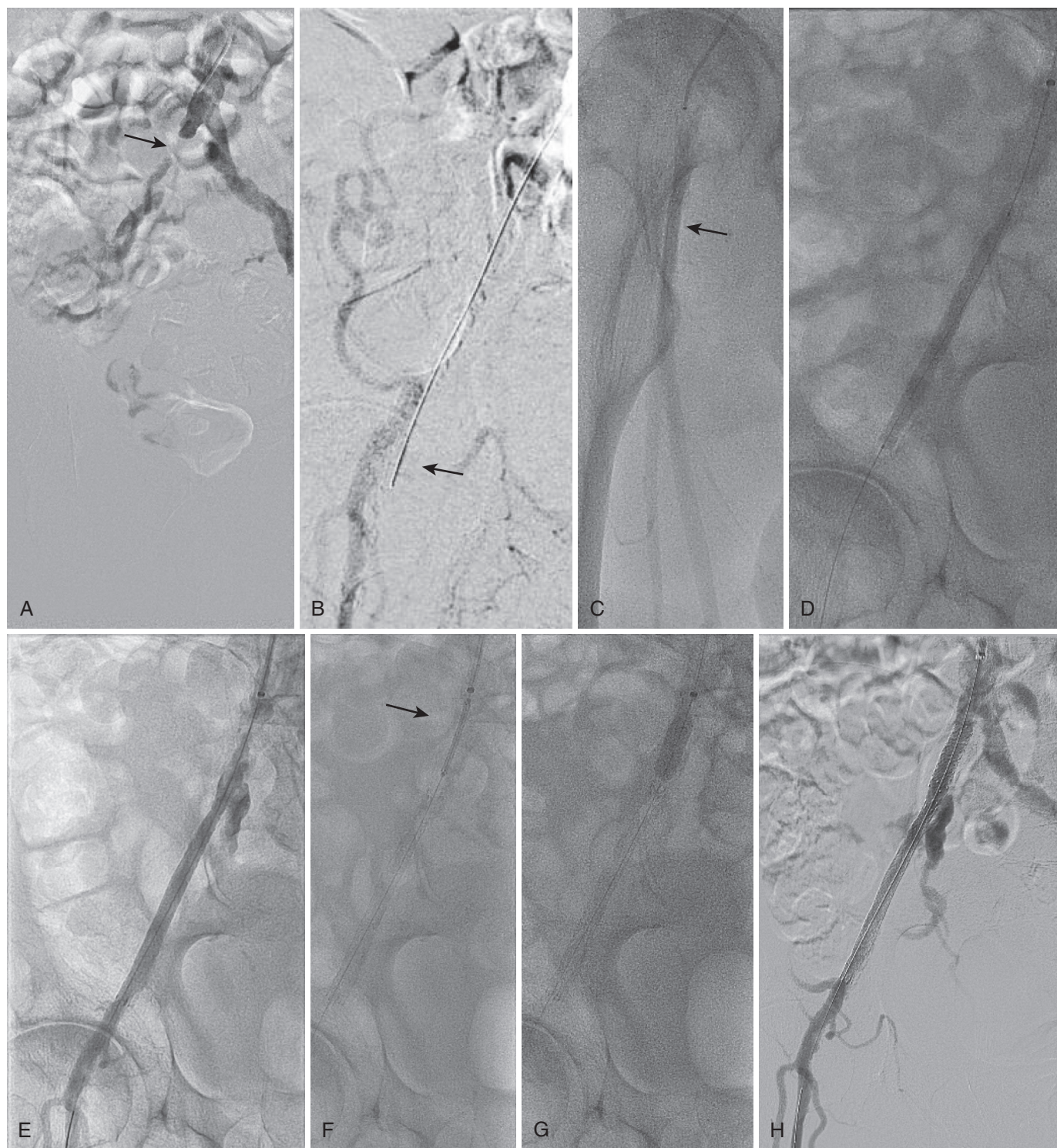


FIGURE 18.5 Brachial approach to a right common and external iliac occlusion. **A**, Angiogram from the brachial artery showing an occlusion at the right common iliac artery (*arrow*). **B**, Wire tip in an extraluminal plane in the external iliac artery (*arrow*). **C**, After wire repositioning, injection distal to the occlusion shows the luminal location of the catheter (*arrow*). **D**, Balloon dilation of the external iliac artery. **E**, External iliac artery after a self-expanding stent used to dilate the artery (because of the close location to the common femoral artery). **F**, Deployment of a proximal balloon-expandable stent at the origin of the right common iliac artery and avoiding the takeoff of the internal iliac artery (*arrow*). **G**, Postdilation of the proximal stent. **H**, Final result showing patent common, internal, and external iliac arteries.

access, closure devices are more difficult to use and tend to have a higher failure rate.

Retrograde access from a more distal artery is useful when antegrade access is unsuccessful (typically in crossing a chronic total occlusion [CTO]) (Figure 18.6 and

Video 18.1).¹¹⁻¹³ Manual compression is required to control hemostasis after the case because the arteries are smaller. The key disadvantage of this approach is the potential to create an ischemic ulcer at the access site if revascularization is unsuccessful.

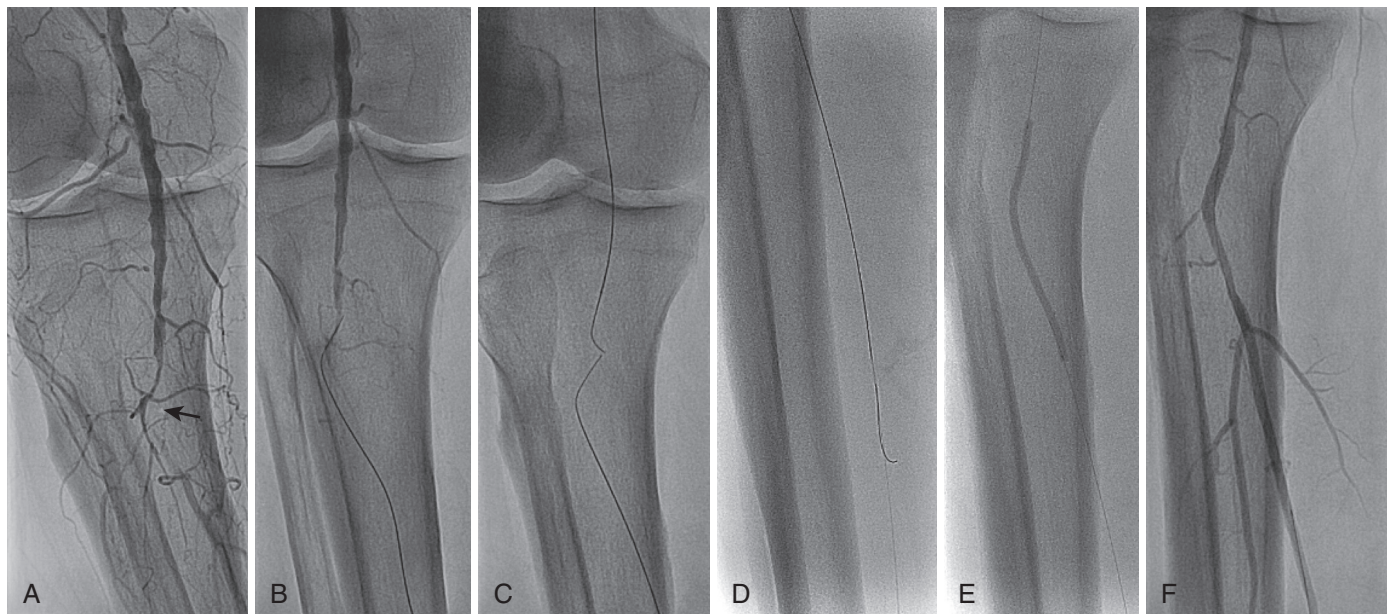


FIGURE 18.6 Antegrade and retrograde approach to an occluded below knee popliteal and posterior tibial artery. **A**, Occluded segment (arrow). **B**, Retrograde wire from the posterior tibial artery accessed at the ankle. **C**, Antegrade and retrograde wires crossing the occlusion. **D**, The antegrade wire crossed the occlusion into the distal posterior tibial artery. **E**, Balloon angioplasty was followed by a short stent in the occluded segment. **F**, Final angiogram. (From Kinlay S, Bhatt DL. Treatment of noncoronary obstructive vascular disease. In: *Braunwald Heart Disease*, ed 12. Elsevier; 2022:864.e2).

Guides and Sheaths

A variety of guides and sheaths are used for lower limb diagnostic cases and interventions. Both are measured in French size (1 Fr = 0.33 mm), but sheath French size refers to the inner diameter, and guide French size refers to the outer diameter. Thus, sheaths have a larger external diameter than the same French guides.

Typical sheaths for the contralateral femoral artery access include the Balkin and Ansel sheaths, which have preformed curves but can be shaped further if required. Conventional short and long sheaths can be used for antegrade femoral artery access, including sheaths with radiopaque tips that show where the tip of the sheath is in relation to the segment being treated. Shuttle sheaths and the longer radial designed systems can be used for access from the arm.

If access is from the contralateral or ipsilateral femoral artery, a multipurpose guide can be directed into the distal superficial femoral or popliteal arteries for interventions below the knee (Figure 18.7 and Video 18.2). This can provide greater support than a femoral sheath and can reduce the amount of contrast required for an intervention. Conventional 0.014-inch coronary balloons or specific peripheral balloons can be used through a 5- or 6-Fr multipurpose guide in this manner.

Wires

A multitude of wires are available to help navigate tortuous stenoses or long CTOs. These include 0.014-inch wires used for coronary artery interventions, which come in a range of tip stiffness and hydrophilic wires. Balloons designed for 0.018-inch wires usually have a low enough profile to be used with 0.014-inch wires, but 0.035-inch

balloons have such a mismatch between the balloon nose and wire that they often do not track well on a 0.014-inch wire. Regular and hydrophilic 0.018-inch wires provide greater support than 0.014-inch wires.

Conventional and stiff 0.035-inch wires (e.g., Amplatz and Rosen wires) provide increased support for directing catheters and guides (e.g., from the contralateral femoral artery). The Wholey wire has a soft tip on a stiff shaft but is often less torquable than a hydrophilic wire. Angled hydrophilic wires can help select arteries for catheters and can be exchanged for stiffer J-wires to direct sheaths into position. Angled hydrophilic wires can be used to cross lesions but can perforate the artery quite easily, so confirmation of location by angiography from multiple views or other methods should be attempted before balloon angioplasty.

Anticoagulation

All interventions and often prolonged diagnostic cases require anticoagulation to prevent thrombus forming on wires and other equipment. Unfractionated heparin is often used at a lower activated clotting time (e.g., 220–250 s) compared with coronary interventions. Heparin is usually the anticoagulant of choice when treating long total occlusions because of the high incidence of wire perforation and the risk of larger perforations that may require immediate reversal of anticoagulation with protamine.

Perforation of the iliac arteries can be catastrophic due to the high volume of blood flow (~200 mL/min at rest) and requires early identification and treatment. Although the recommended dose of protamine is approximately 10 mg per 1000 U of heparin used (and up to a maximum of 50 mg), often lower doses are successful in stopping



FIGURE 18.7 Antegrade access for balloon angioplasty to a totally occluded anterior tibial artery to treat a nonhealing ulcer of the anterolateral foot using a multipurpose guide in the popliteal artery for support. **A**, Baseline angiogram showing occlusion of the anterior tibial artery (*arrow*). **B**, A 0.014-inch wire entering the occluded artery. **C**, Angioplasty of the distal anterior tibial artery with a 2.0- × 80-mm balloon. **D**, Angiogram after dilating the anterior tibial artery with a 2.0-mm balloon. **E**, Dilation of the distal artery with a 3.0-mm balloon. **F**, Dilation of the proximal anterior tibial artery with a 3.0-mm balloon. **G**, Final angiogram of the proximal anterior tibial artery. **H**, Final angiogram of the foot showing a patent dorsalis pedis artery (DP) and posterior tibial artery (PT) with a restored pedal arcade.

bleeding, particularly when used with low-pressure balloon tamponade near the site of perforation. If unsuccessful, covered stents can be used to treat perforation (see later discussion).

Reentry Devices

Reentry devices are designed to locate the distal true lumen after dissecting through a CTO.^{11,12} All of these devices work on a principle that if a guidewire dissects down the side of a plaque into a plane beyond the distal cap, the reentry catheter will direct a guidewire into the true lumen. After accessing the distal artery lumen, the reentry device is removed and followed by conventional angioplasty, stenting, or both. These devices await formal testing against standard interventional techniques to cross occlusions.

The Pioneer Plus catheter (Philips Electronics; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K081804>) has a multiple array intravascular ultrasound at the end of the catheter. This is connected to a Philips intravascular ultrasound system and is used to image the true lumen. The catheter is rotated until the distal

true lumen appears at the 12 o'clock position of the ultrasound image, which corresponds to the direction the curved needle at the tip of the device will deploy (Figure 18.8). When the needle is in the true lumen, a 0.014-inch wire can be advanced through the needle into the true lumen.

The Outback Elite (Cordis; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K150836>) has an angled needle housed at the tip of a catheter with an L-shaped tip under fluoroscopy. The catheter is advanced into a dissection plane adjacent to the distal true lumen and the catheter turned until the L-shaped marker is directed toward the lumen. In an orthogonal view, the tip should have a T-shape overlapping the distal true lumen. At this point, a distal needle is deployed into the true lumen, and an 0.014-inch wire is advanced through the needle into the true lumen.

The Crossboss and Stingray balloon (Boston Scientific; https://www.accessdata.fda.gov/cdrh_docs/pdf10/K102725.pdf) are coronary CTO devices that dissect into the plaque and allow the Stingray balloon to be positioned in the subintimal plane beyond the occlusion. The balloon has a central wire port and two side ports facilitating distal

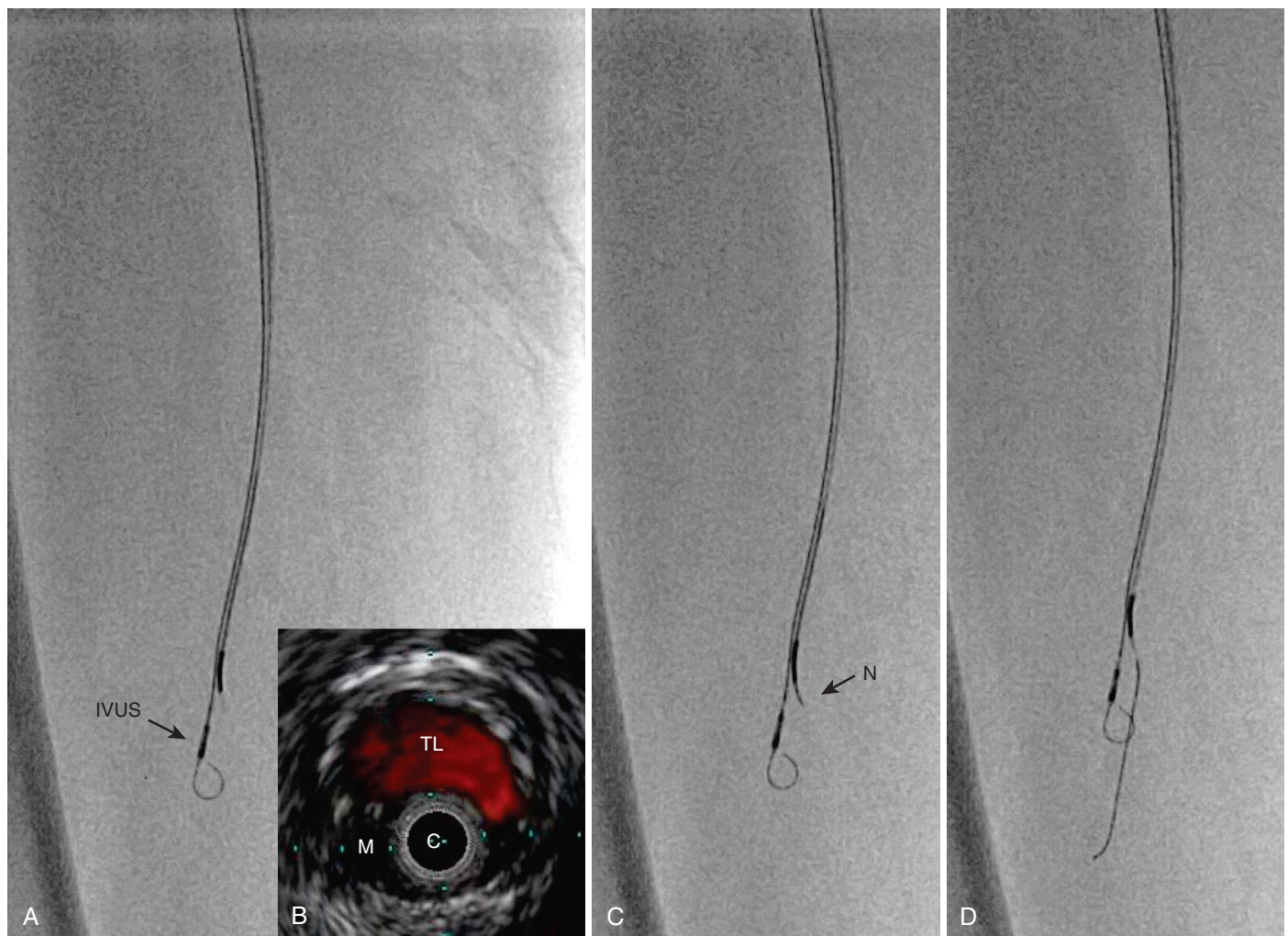


FIGURE 18.8 Pioneer catheter used to select the true lumen of a total occlusion of the superficial femoral artery. **A**, Pioneer catheter in a dissection plane just beyond the distal cap of the total occlusion. The intravascular ultrasound (IVUS) element of the catheter images the true lumen. **B**, IVUS image showing the catheter (C) in the media (M) of the artery imaging the true lumen (TL) with the aid of the ChromaFlo function showing moving blood in the lumen. **C**, The needle (N) is deployed into the true lumen. **D**, A 0.014-inch guidewire is advanced through the needle into the true lumen.

reentry with a hydrophilic wire. The Enteer reentry system (Medtronic; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm?lid=686150&lpcd=PDU>) uses a similar concept with a flat balloon with two side-exit ports. In both cases, fluoroscopy is used to avoid directing the wire to the port adjacent to the outer artery wall and instead chooses the exit port adjacent to the true lumen.

Other Chronic Total Occlusion Devices

A number of devices are designed to assist crossing total occlusions that often have tough entry and exit caps. Like the reentry devices already discussed, case reports and series describe their use, but their value over conventional wire crossing techniques is untested. Reentry devices may be needed with CTO devices if the latter do not enter the distal lumen.

The Crosser CTO system (Bard; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K161208>) uses a nitinol wire inserted into the proximal cap of an occlusion. The distal end of the wire is connected to an external transducer that generates high-frequency vibrations down the wire to move the tip through an occlusion. The PowerWire catheter (Baylis Medical Co.; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?id=K101615>) uses radiofrequency ablation to ablate plaque in a CTO.

The TruePath CTO (Boston Scientific; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K140288>) is an 0.018-inch wire with a diamond-encrusted tip that is connected to an external motor drive to burr through occlusions. The Viance catheter (Medtronic) uses a similar design with an atraumatic tip designed to blunt dissect down a plane in the artery media.

The Kittycat2 and Wildcat catheters (Avinger; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K120273>) have a rotating screw on the tip and are connected to an external motor drive to drill through an occlusion. The Ocelot catheter (Avinger) combines this design with a cross-sectional optical coherence tomography (OCT) imaging system to avoid perforating the artery.

Balloon Angioplasty

Balloon angioplasty remains the standard revascularization technique for most interventions in the lower limbs (Figure 18.9), although it is often accompanied by stenting, particularly for long lesions. Although coronary 0.014-inch platform balloons can be used to cross lesions, they are generally too short for most lesions and less pushable than dedicated peripheral balloons.

Peripheral balloons are available in 0.014-, 0.018-, and 0.035-inch platforms. Smaller diameter balloons are available

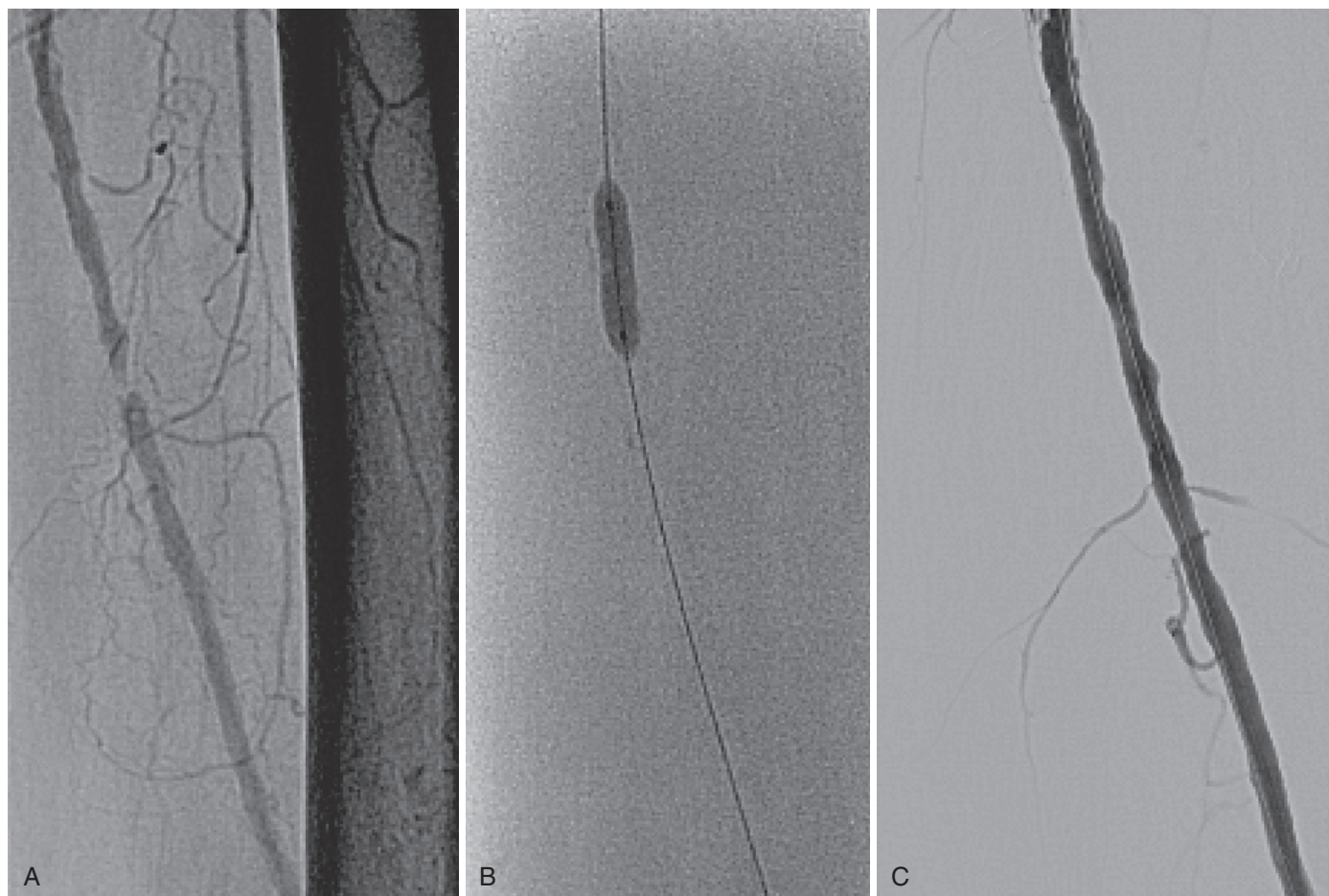


FIGURE 18.9 Treatment of a mid superficial femoral artery stenosis (A), with balloon angioplasty alone (B), with an excellent final result (C). (From Kinlay S, Bhatt DL. Treatment of noncoronary obstructive vascular disease. In: *Braunwald Heart Disease*, ed 12. Elsevier; 2022:861).

in 0.014- and 0.018-inch platforms and are useful in the smaller tibial arteries (generally 2- to 4-mm-diameter arteries). Larger diameter balloons are available in the 0.018- and 0.035-inch platforms, generally for treating iliac and femoral arteries. Balloons designed for radial access are rapid exchange and use a longer 200-mm delivery device. Cutting or scoring balloons have wires or blades that concentrate the force of expansion at the wire or blade to theoretically generate a controlled dissection or crack intravascular calcium.

Deflator kits available for coronary interventions are suitable for inflating peripheral balloons. Because larger diameter balloons are used (compared with coronary interventions), the contrast used to dilate the balloons is usually more dilute (a 1:3 or 1:4 contrast:saline ratio). This allows faster inflation and deflation times and is usually an adequate density to visualize under fluoroscopy.

Angioplasty increases the arterial lumen through positive remodeling (acutely via expansion of the whole artery) and controlled dissections in the plaque and intima. Larger dissections that limit flow or have visible flaps greater than 50% of the lumen diameter increase the risk of abrupt closure in the proceeding 24 to 48 hours. Prolonged inflations are typical (1–2 minutes) and may reduce large dissection. Over days to several months, angioplasty promotes a healing response associated with neointima produced largely by proteoglycan production from vascular smooth muscle cells. Restenosis over several months occurs by excessive neointima and negative remodeling of the whole artery.

Drug-Coated Balloons

Drug-coated balloons offer a lower rate of restenosis than noncoated balloons. These balloons are coated in drugs

of the taxane class (e.g., paclitaxel), usually mixed with a molecule that acts as a detergent to promote release from the balloon and distribution into the injured arterial intima after balloon angioplasty. They are used at the end of an intervention, as the drug is removed off the balloon with a single inflation. Results compared with conventional balloon angioplasty in the lower extremities show less restenosis and greater long-term patency of the femoral and tibial arteries when used as the initial intervention or as treatment for restenosis.¹³ Concerns of increased mortality with these devices are still debated (see the Controversy Over Paclitaxel Coated Balloons and Stents section).

Stents

The two stent designs for the lower extremity arteries are balloon-expandable or self-expanding. Stent therapy requires aspirin and a thienopyridine (e.g., clopidogrel), although the evidence for dual antiplatelet therapy is derived largely from the coronary stent literature. Balloon-expandable stents are made from alloys of steel and titanium or other metals (Figure 18.10). These provide a high degree of radial strength and are easier to deploy accurately (e.g., at ostial locations) compared with self-expandable stents, but they can be compressed by external force. For this reason, balloon-expandable stents are often used for iliac artery lesions.

Self-expanding stents are now largely made from nitinol (Figure 18.11). Their key advantage is their ability to recoil back to their baseline diameter after external compression, and for this reason, they are used outside the torso and where there are greater torsion and compression forces on the artery (e.g., the superficial femoral artery). However, self-expanding stents can be kinked or fractured

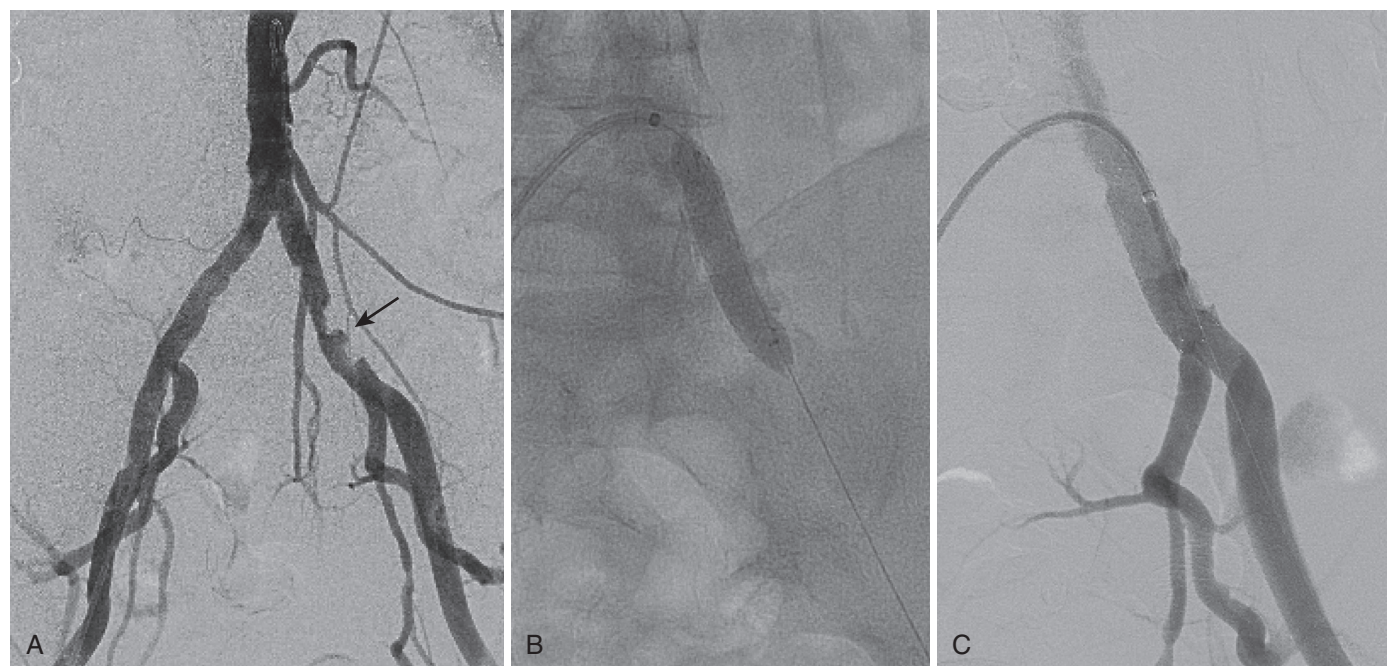


FIGURE 18.10 Treatment of left common iliac stenoses with a balloon-expandable stent from the contralateral right femoral artery. **A**, Serial stenoses in the left common iliac artery (arrow). **B**, Balloon expandable stent deployment. **C**, Final angiogram. (From Kinlay S, Bhatt DL. Treatment of noncoronary obstructive vascular disease. In: Braunwald Heart Disease, ed 12. Elsevier; 2022:861).

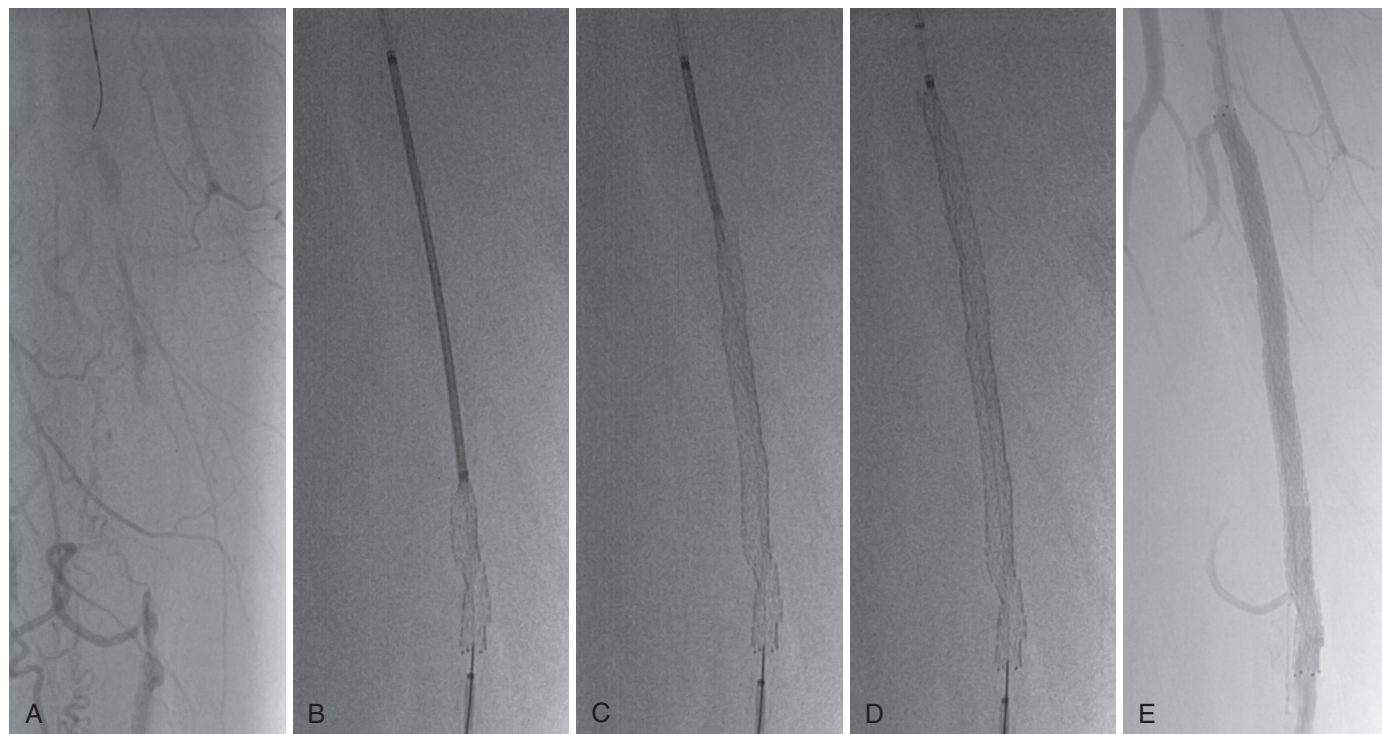


FIGURE 18.11 Treatment of a superficial femoral artery occlusion with a self-expandable nitinol stent. **A**, A wire approaches the occluded segment. **B–D**, The delivery catheter is pulled back to release the self-expanding stent. **E**, Final angiogram. (From Kinlay S, Bhatt DL. Treatment of noncoronary obstructive vascular disease. In: *Braunwald Heart Disease*, ed 12. Elsevier; 2022:860.e1).

with excessive flexion and torsion, particularly over joints, for example, the popliteal artery. These stents tend to move on deployment and are therefore more difficult to use at ostial locations. Self-expanding stents that cover a large branch vessel (e.g., jail the profunda artery when treating a proximal superficial femoral lesion) are difficult to recover because dilation through the stent struts is ineffective because of strut recoil. For these reasons, self-expanding stents are avoided where possible over the knee and hip joints and are used in these locations only in cases when surgery is a prohibitive risk. A poor angiographic result requiring stenting is usually interpreted to mean dissection or recoil with poor flow (abnormally slow flow velocity) or a flap visibly extending beyond 50% of the lumen diameter.

Covered Stents

Stents covered in a polytetrafluoroethylene (PTFE) jacket are available in both balloon-expandable and self-expanding stent formats (Figure 18.12 and Video 18.3).^{6,8} These are particularly useful in treating arterial perforations to prevent exsanguination or compartment syndromes. They are sometimes promoted as causing less restenosis (by excluding neointima), but the studies used to make this claim may be too short in duration to assess this outcome if restenosis is a longer process with covered stents.⁶ Covered stents also risk covering important branch arteries or collaterals and predispose to ALI in the case of stent occlusion (Figure 18.13; see part L). Stent thrombosis may also be higher with covered stents. It is uncertain if

heparin-coated covered stents prevent stent thrombosis in longer term follow-up.

Drug-Eluting Stents

Drug-eluting self-expanding stents using polymer¹⁴ or polymer-free coating¹⁵ of paclitaxel offer lower rates of restenosis than bare-metal self-expanding stents. Freedom from repeat revascularization was 66% with polymer-coated drug-eluting stent versus 43% with bare-metal stents at 5 years in the Zilver study,¹⁴ with similar efficacy at 3 years in a single-arm study using the polymer-free drug-eluting stent.¹⁶ In one trial, drug-eluting self-expanding stents had similar patency and target lesion revascularization rates at 12 months with lower complication rates and shorter lengths of hospital stay than surgical bypass with prosthetic graft.¹⁷ The duration of dual antiplatelet therapy required for these stents is uncertain, but recent trials generally used 2 to 6 months of treatment.^{14,15}

Drug-eluting balloon-expandable stents developed for the coronary arteries can often be used for bailout situations such as major dissection after below-knee balloon angioplasty (see Figure 18.6F). In this situation, if the lesion is focal (<30 mm), drug-eluting balloon-expandable stents can reestablish flow and give acceptable patency up to 1 year.⁶ However, they are subject to compressive forces, particularly with multiple overlapping or distal tibial stents, and their use is generally reserved for proximal tibial revascularization with CLI when major amputation is being prevented.

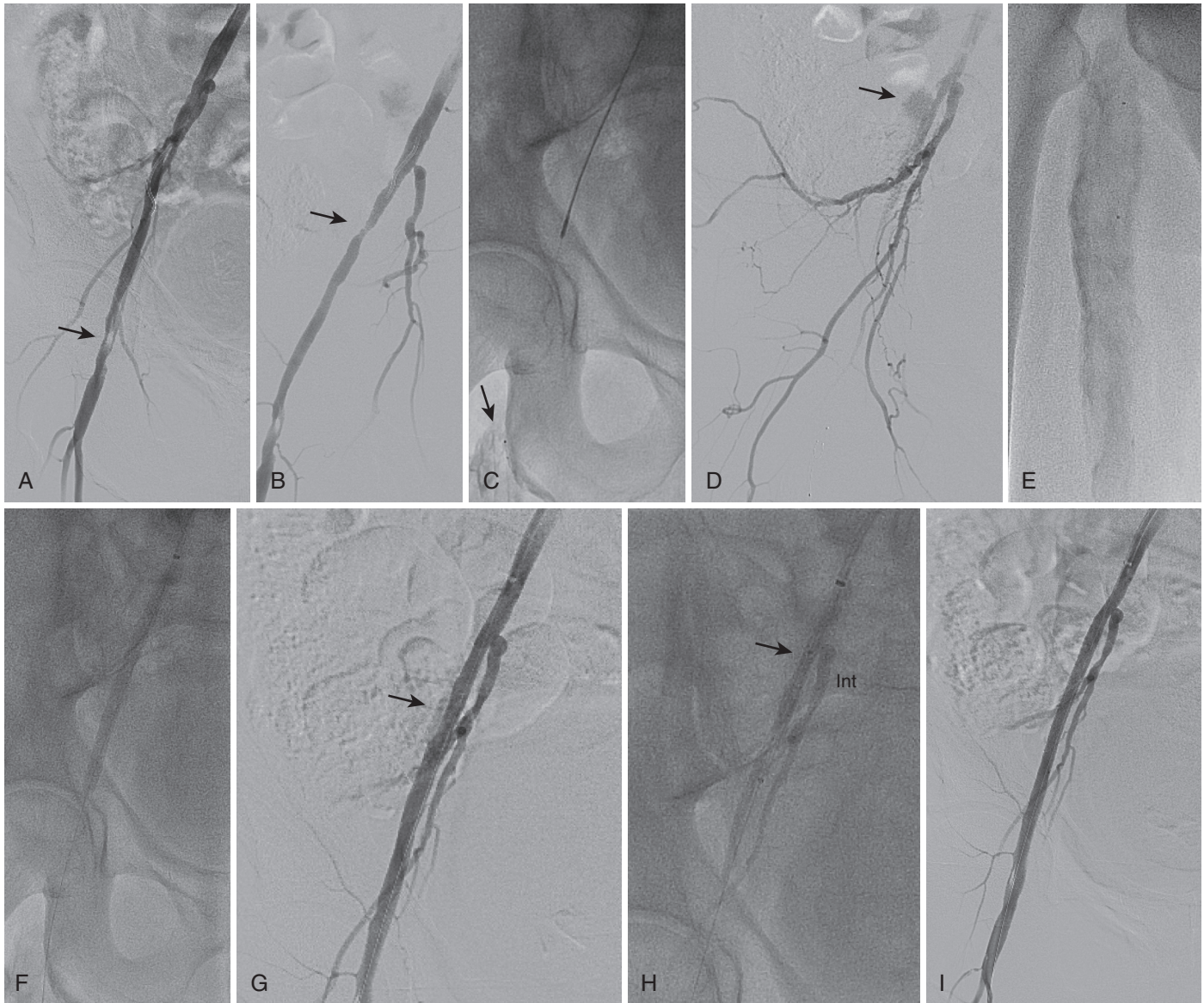


FIGURE 18.12 Treatment of sheath or guide perforation. **A**, The target lesion was a stenosis in the common femoral artery (arrow). **B**, Oblique angiogram showing a more proximal stenosis in the external iliac artery (arrow). **C**, Jetstream run of the common femoral lesion. Note the contrast extravasation, which was appreciated at the end of the Jetstream run (arrow). **D**, Angiogram showing a perforation of the proximal external iliac artery, likely caused by the sheath perforating the artery at the more proximal lesion. **E**, Contrast tracking in the extravascular tissues around the superficial femoral artery in the upper thigh. **F**, Balloon tamponade of the perforated external iliac lesion at low pressure with a 7.0- × 100-mm balloon. **G**, A smaller amount of extravasation of the dye at the perforation site (arrow). **H**, Placing a 7.0- × 38-mm covered stent in the proximal external iliac using an oblique fluoroscopic image to position the proximal stent delivery marker (arrow) at the ostium of the external iliac artery so it does not cover and exclude the internal iliac artery. **I**, Final angiogram showing no perforation and successful balloon angioplasty alone of the common femoral artery. *Int*, Internal iliac artery.

CONTROVERSY OVER PACLITAXEL-COATED BALLOONS AND STENTS

In 2018 and 2020 two group-level meta-analysis of randomized trials reported that patients treated with paclitaxel-coated devices had higher mortality rates 2 to 5 years after their procedure compared with those treated with non-coated devices.^{18,19} In response to these reports, investigators reported patient-level long-term outcomes data refuting the higher late mortality risk 3 to 5 years after treatment with drug-coated devices in the femoral-popliteal artery.²⁰⁻²² Analyses of large administrative databases from the United States²³ and Germany²⁴ suggested lower mortality rates and amputation at 5 years with drug-coated devices for CLI

and claudication. Furthermore, late mortality risks were not observed with drug-coated balloons used to treat patients with coronary artery disease.²⁵ Currently, the Food and Drug Administration recommends discussing potential long-term risks with patients and reserving drug-coated devices to cases with high risk of restenosis (e.g., long lesions). Drug-coated devices using the limus class of drugs are currently being developed.

Atherectomy

Although various debulking and atherectomy devices may change the distensibility of arteries, there is little evidence that these devices provide better long-term patency over

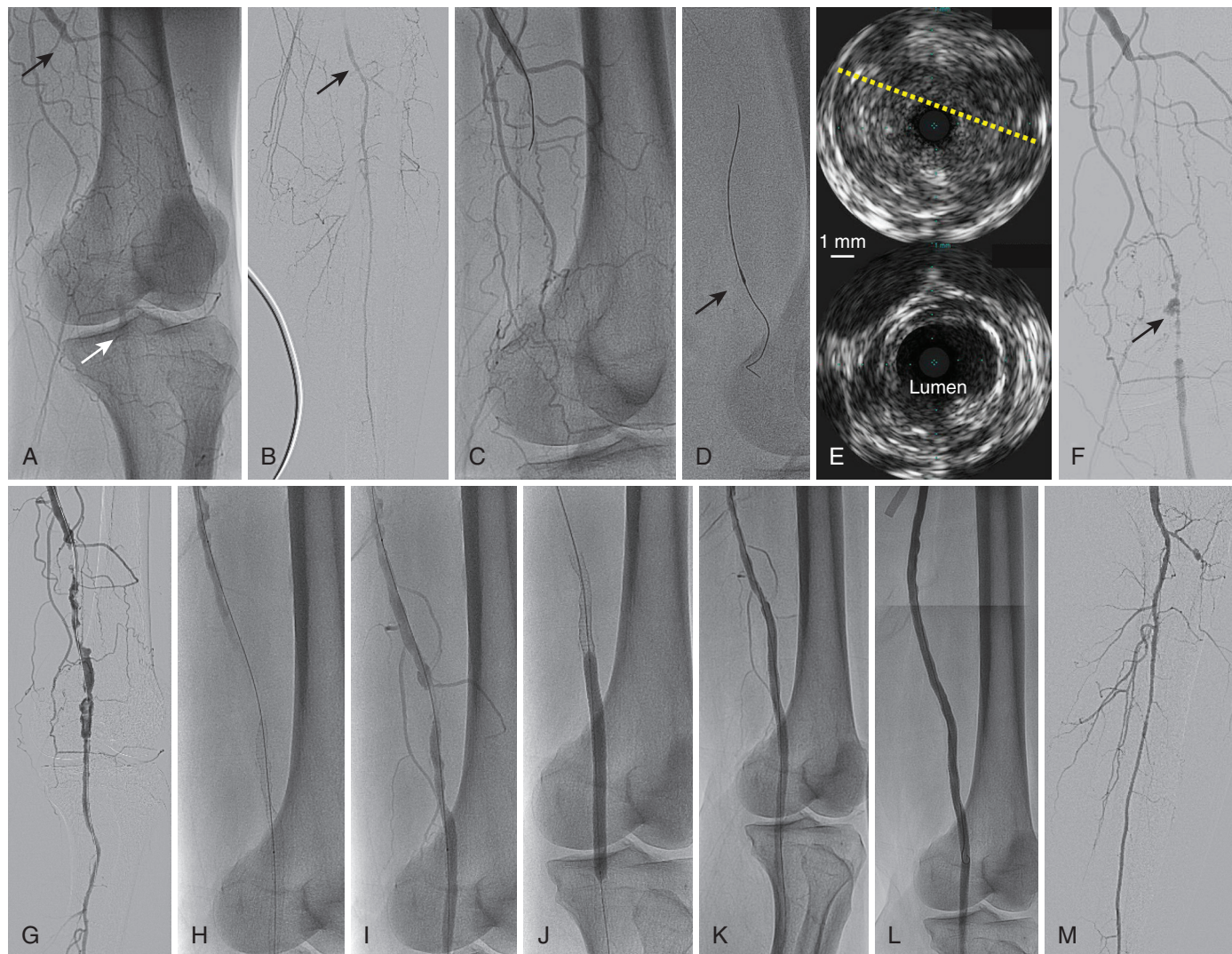


FIGURE 18.13 Endovascular treatment of a thrombosed popliteal aneurysm for a patient at high surgical risk. **A**, Occluded above-knee popliteal artery (black arrow), with reconstitution of the below-knee popliteal artery by collaterals (white arrow). **B**, Distal runoff into a peroneal artery (arrow). The anterior and posterior tibial arteries are occluded. **C**, Wire in the proximal occlusion. **D**, Intravascular ultrasound (IVUS) catheter placed in occlusion to assess the popliteal artery. **E**, IVUS images. Upper image showing a thrombosed popliteal aneurysm (yellow line indicates a 9-mm vessel diameter). Lower image showing reentry into the distal lumen of the below-knee popliteal artery. **F**, Thrombus in the popliteal artery (arrow). **G**, Twenty-four hours after catheter-directed thrombolysis. The angiogram shows extensive residual thrombus in an aneurysmal popliteal artery. **H**, Placement of a self-expanding covered stent in the mid to distal popliteal artery. **I**, Angiogram showing residual disease proximal to the stent. **J**, Postdilation after a second, more proximal covered self-expanding stent. **K**, Angiogram showing thrombus at the proximal margin of the stents. **L**, Final angiogram after a third proximal stent placed. Note the loss of collaterals. The white arrows indicate the top of the patella and the tibial epiphyseal plate where the popliteal artery is particularly subject to bending. **M**, Final angiogram of the distal popliteal artery and peroneal artery below the knee.

successful balloon angioplasty. Therefore, atherectomy is largely used as adjunctive therapy along with balloon angioplasty, stenting, or both.²⁶ This strategy can be particularly useful for calcified lesions that may be difficult to expand by balloon or stent or in arteries over joints where atherectomy may reduce the risk of flow-limiting dissection with balloon angioplasty.

Rotational atherectomy uses a rotating burr to grind off particles of plaque that are either aspirated or small enough to go through capillaries and be removed by the reticular endothelial system. These include the Rotablator (Boston Scientific; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K121774>), which was developed for coronary atherectomy but may be of use in the smaller distal arteries of the lower extremity (Figure 18.14);

the Jetstream (Boston Scientific; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K130637>), which aspirates debris (Figure 18.15); and the Diamondback 360 peripheral orbital atherectomy (Cardiovascular Systems; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K203008>; Video 18.4), which are wires with an eccentrically mounted diamond-encrusted burr to encourage a larger orbital cutting arc when the wire is rotated at high speed.

The directional atherectomy devices include the TurboHawk or Silverhawk (Medtronic; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K170191>), which has a cutting window that can be oriented to different directions before cutting and collecting plaque in the nose cone of the device (Figure 18.16).

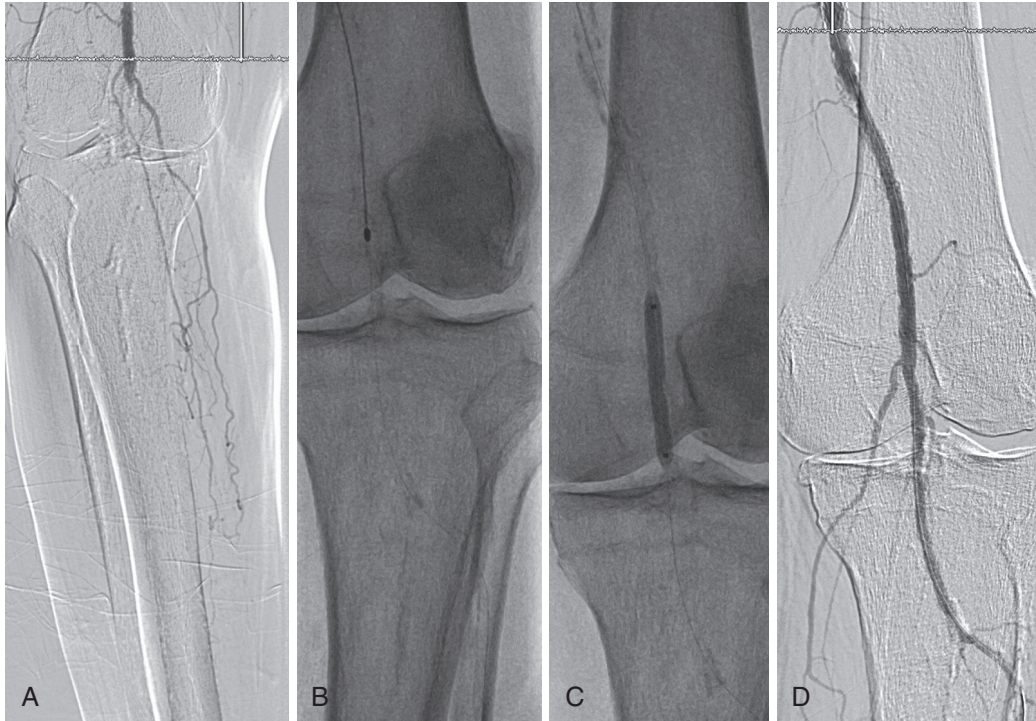


FIGURE 18.14 Occluded popliteal artery treated by rotablation and balloon angioplasty. **A**, Occluded artery. **B**, Rotaburr during rotablation. **C**, Balloon angioplasty. **D**, Final result. (From Kinlay S, Bhatt DL. Treatment of noncoronary obstructive vascular disease. In: *Braunwald Heart Disease*, ed 12. Elsevier; 2022:863.e1).

All atherectomy devices have a tendency to embolize atheroma even if they are designed to aspirate or collect atheroma. Long-segment atherectomy has greater risks of embolizing small material into the microcirculation, potentially leading to slow flow and CLI. This can be prevented by deploying a distal filter embolic protection with some devices to capture embolized debris.

In the event embolization occurs, large emboli can be removed by catheter aspiration or broken up by balloon angioplasty. Small-vessel embolization with slow flow may respond to bolus doses of microvascular dilators such as nitroprusside (100–300 μ g).

Laser Atherectomy

Excimer laser atherectomy uses high-energy monochromatic ultraviolet light to vaporize tissue in contact with the catheter tip and debulk de novo and restenotic lesions.²⁶ Laser ablates tissue by breaking down mechanical carbon-carbon bonds in tissue (photoablation), thermal energy effects (photothermal), and generation of a vapor bubble that produces kinetic energy to disrupt tissue (photomechanical). Laser catheters are advanced over a 0.014-inch guidewire (Figure 18.17 and Video 18.5). Because blood absorbs some of the laser energy, laser runs are accompanied with a slow saline flush, which also constrains the size of the vapor bubble to avoid excessive injury to the artery. The repetition rate of pulses and the energy delivered per pulse (fluence) are adjusted to increase the ablation. Some operators use a short puff of dilute contrast with laser runs to increase the size of the vapor bubble, but this can increase the risk of injury to the artery or slow flow.

Intravascular Lithotripsy

Intravascular lithotripsy (Shockwave Medical; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?start_search=1&productcode=PPN&number=&applicant=Shockwave%20Medical%2C%20Inc%2E) uses a balloon with up to five pressure-emitting nodes along the balloon shaft to generate waves of pressure into the artery wall during low pressure balloon inflation. The pressure wave creates microfractures in intravascular calcium to permit arterial dilation at lower pressure (Figure 18.18 and Video 18.5). A meta-analysis of cohort studies indicate improvements in stenosis severity with acute adverse events of dissection, perforation, no reflow, or embolization of 1% to 2% of cases.²⁷ This technology may be particularly useful in heavily calcified larger arteries such as iliac or common femoral arteries.

Brachytherapy

Brachytherapy in the lower limbs typically requires gamma radiation because of the larger distance between the delivery catheter and the wall of most lower extremity arteries (compared with coronary arteries). This technique is sometimes used to treat diffuse in-stent restenosis, but the extensive shielding and collaboration with radiation therapists make this technically difficult in most centers. The clinical effect of brachytherapy is not well studied, and the potential for drug-eluting balloons to be a much easier technology for this indication has decreased its popularity.

Catheter-Based Thrombolysis

Thrombosis of a major lower limb artery causing acute or CLTI/CLI can be treated successfully by catheter-based

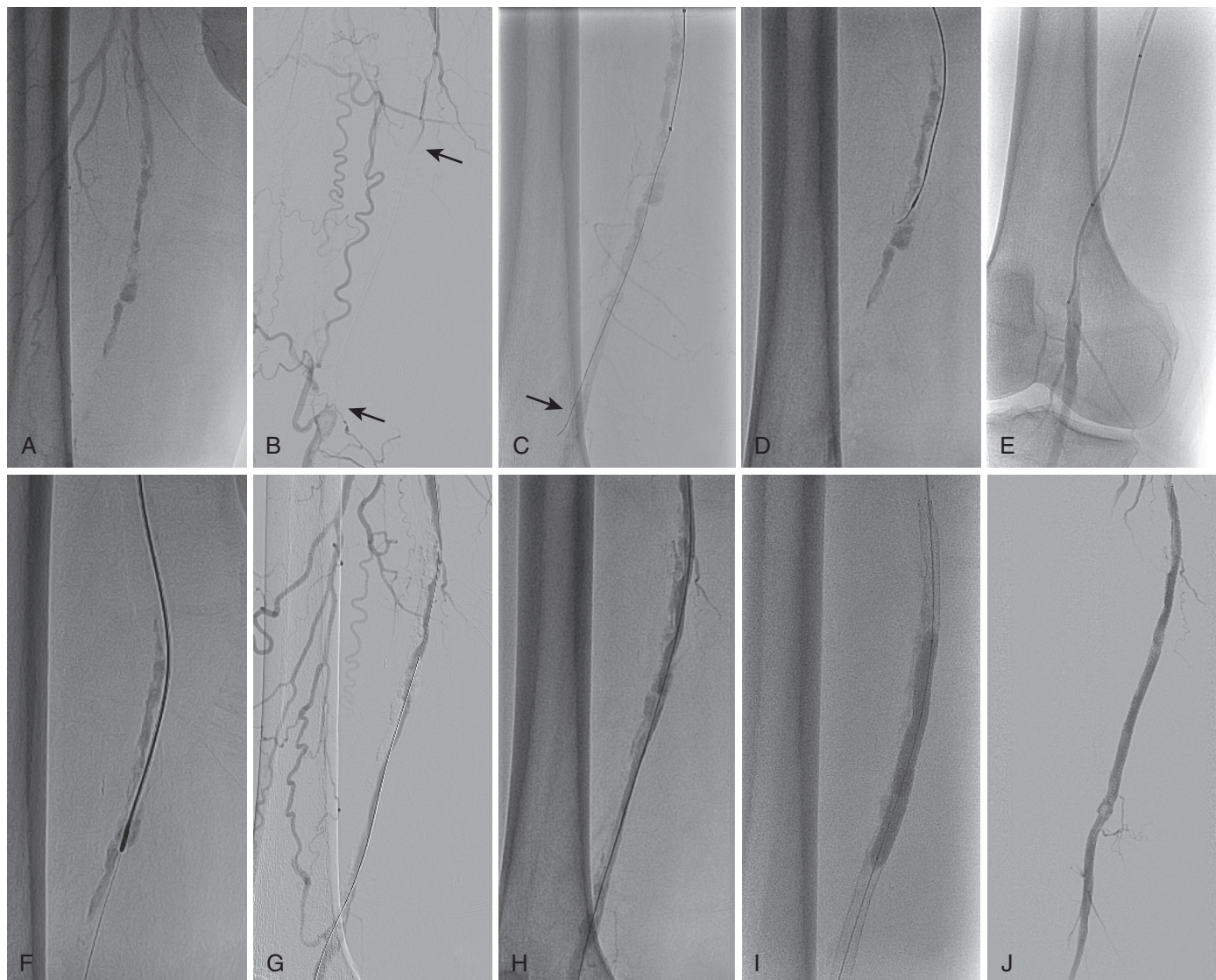


FIGURE 18.15 Rotational atherectomy in a heavily calcified total occlusion of the superficial femoral artery. **A**, Fluoroscopy without contrast shows heavy calcification. **B**, Digital subtraction angiography showing a total occlusion between the *two arrows* and distal reconstitution by collaterals from the profunda femoral. **C**, Attempt to cross the lesion with a wire leads to the wire tip in an extraluminal plane (*arrow*). **D**, Intravascular ultrasound used to locate the most distal true lumen in the occlusion (see [Figure 18.19](#)). **E**, Injection through a support catheter demonstrating successful reentry into the true lumen in the above knee popliteal artery. **F**, Rotational atherectomy with a Jetstream device. **G**, Angiogram after atherectomy. **H**, Angiography after balloon angioplasty. **I**, Postdilating a self-expanding stent. **J**, Final result.

thrombolysis using infusions of thrombolytic agents (e.g., recombinant tissue plasminogen activator [tPA]).^{1,2}

Catheter-based infusion of thrombolytic drugs over 12 to 48 hours is best achieved after inserting a multiple hole infusion catheter over a wire into the thrombosed segment ([Figure 18.19](#) and [Video 18.6](#)). The wire is removed, and a valve at the tip closes to prevent the thrombolytic agent from exiting the end of the catheter. Instead, the thrombolytic agent infuses through multiple side holes over a 100- to 200-mm length of the catheter directly into the thrombus. An initial bolus of 2 to 6 mg of tPA is given through the catheter, and then a 1- to 2-mg per hour infusion over 12 to 48 hours is given. Usually, 12 to 24 hours is adequate, with longer infusions increasing the risk of depleting fibrinogen and increasing bleeding from the access site or elsewhere.⁴ Low-dose intravenous

anticoagulation with heparin is often used concurrently. Systemic concentrations of fibrinogen levels of less than 100 mg/dL may indicate a higher risk of bleeding and the need to stop thrombolysis.

Absolute contraindications to thrombolysis include (1) a cerebrovascular event less than 2 months previously, (2) active bleeding, (3) gastrointestinal bleeding less than 10 days previously, and (4) neurosurgery (intracranial or spinal surgery) or trauma less than 3 months previously. Relative contraindications include (1) cardiopulmonary resuscitation less than 10 days previously, (2) nonvascular surgery or trauma less than 10 days previously, (3) uncontrolled hypertension (sustained systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg), (4) puncture of a noncompressible vessel, (5) intracranial tumor, and (6) recent eye surgery.²

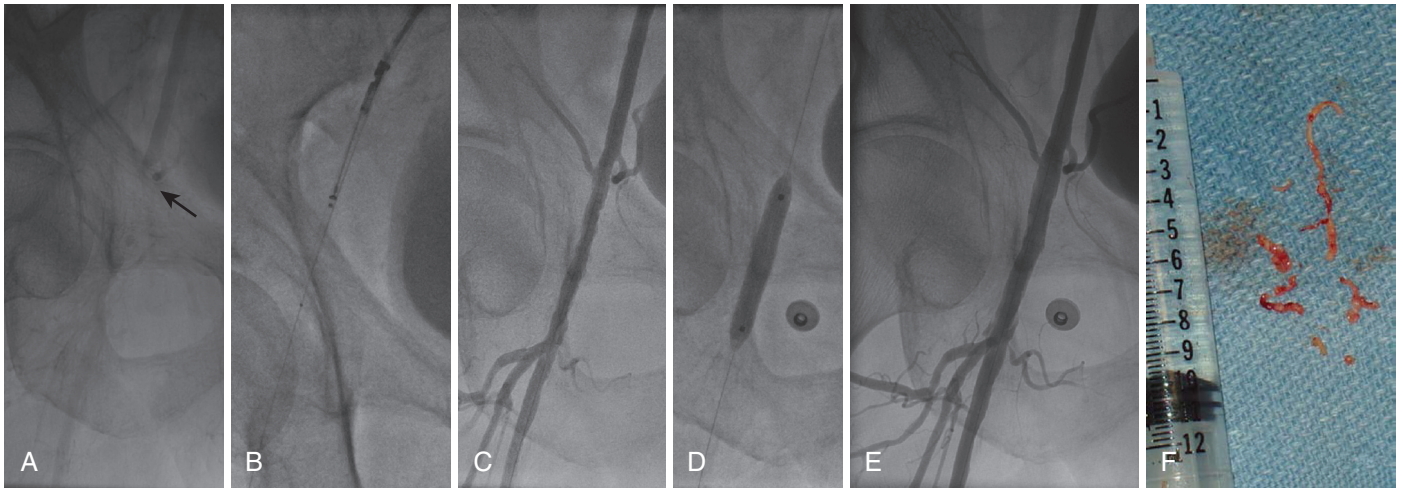


FIGURE 18.16 Common femoral artery occlusion treated with directional atherectomy. **A**, Occlusion in the right common femoral artery (arrow). **B**, Directional atherectomy catheter. **C**, After eight cutting runs. **D**, Adjunctive balloon angioplasty. **E**, Final angiogram. **F**, Atheromatous material removed by the atherectomy device. (From Kinlay S, Bhatt DL. Treatment of noncoronary obstructive vascular disease. In: *Braunwald Heart Disease*, ed 12. Elsevier; 2022:863.e2).

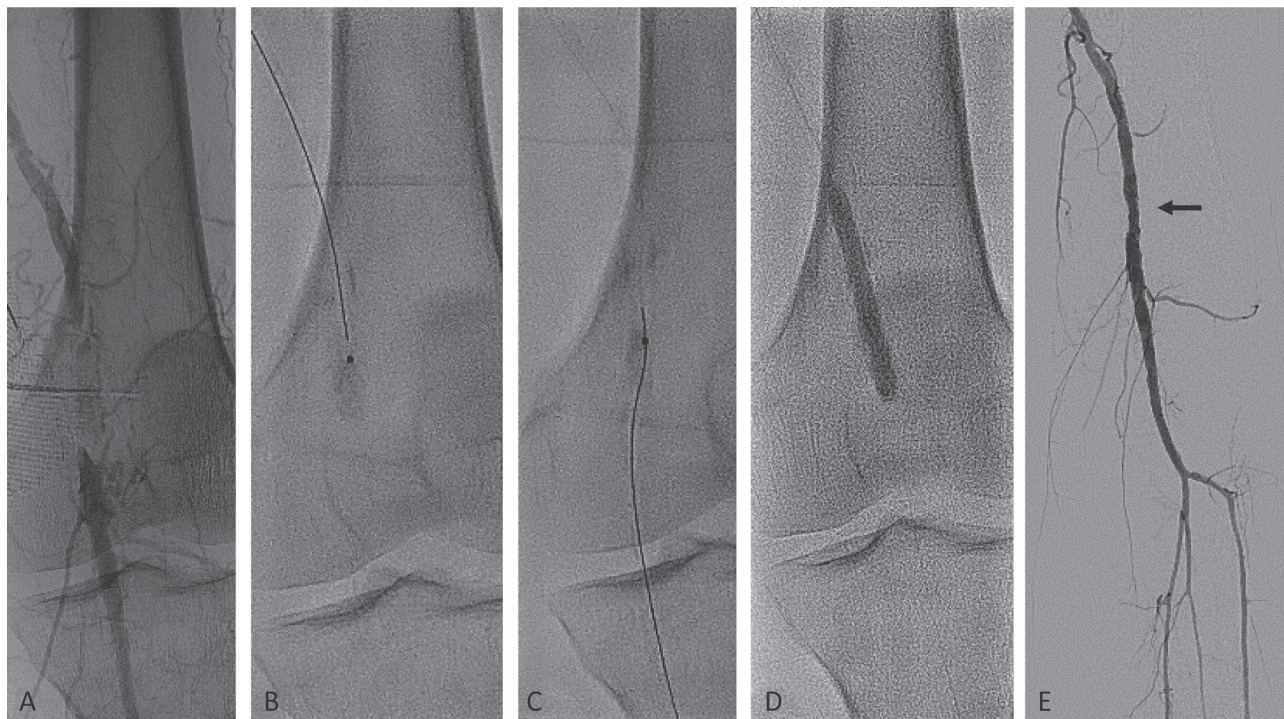


FIGURE 18.17 Laser atherectomy of an occluded heavily calcified popliteal artery. **A**, Occluded popliteal artery. **B**, Laser catheter positioned over a heavily calcified proximal cap of the occlusion. **C**, The laser fractured the cap allowing a 0.014-inch wire to cross the lesion. **D**, After serial balloon dilations, a 6.0- × 40-mm balloon inflation dilates the lesion. **E**, Final result with good tibial artery flow and the arrow indicating the treated segment. (From Kinlay S, Bhatt DL. Treatment of noncoronary obstructive vascular disease. In: *Braunwald Heart Disease*, ed 12. Elsevier; 2022:863.e2).

Mechanical and Aspiration Thrombectomy

In cases when a patient may not stay on bed rest; when a lower dose of thrombolytic agent is preferred, or when the time required for catheter-based infusion may jeopardize the viability of a limb, mechanical and manual aspiration techniques are available.

Manual aspiration catheters use a rapid-exchange port to deliver the catheter to the thrombus and have a larger aspiration port to aspirate the thrombus using a large syringe (Export Advance; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmnm.cfm?id=K152335> and Pronto

catheter; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmnm.cfm?ID=K083784>). These catheters work better with smaller rather than large thrombi, and aspiration thrombectomy using a number of catheters. The AngioJet (Boston Scientific; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpMN/pmnm.cfm?ID=K960970>) uses a Venturi effect to aspirate thrombus and debris from arteries (Figure 18.20). However, in the pulse-spray mode, aspiration is blocked, and the catheter sprays a solution of thrombolytic agent into the thrombosed artery (e.g., 10 mg of tPA in 50 mL of saline or 10–20 mg of TNK in 50 mL of

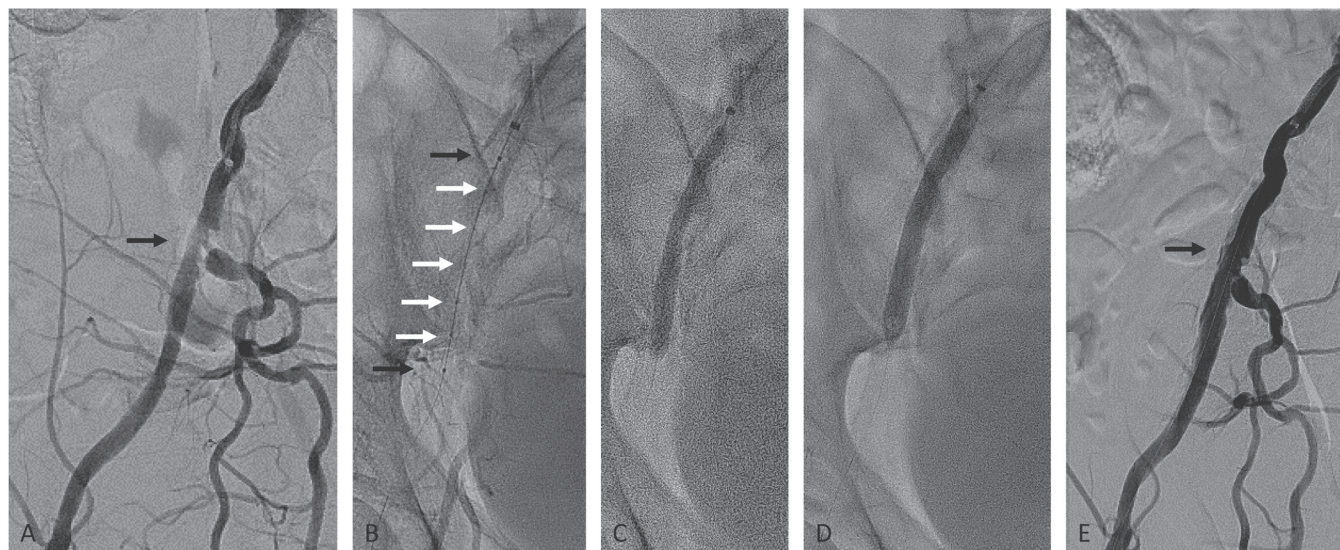


FIGURE 18.18 Intravascular lithotripsy of a calcified right iliac lesion. **A**, Lesion at the distal right common iliac artery (arrow). **B**, Lithotripsy balloon in place over the lesion. Black arrows indicate the proximal and distal markers of the balloon, and white arrows indicate the pressure-emitting nodes. **C**, Low-pressure balloon inflation (2 atm) showing an initial waist in the balloon. **D**, After 300 lithotripsy pulses, the compliance of the artery is improved with expansion of the balloon. **E**, Final result showing good lesion expansion. There was a small dissection cap (arrow) that did not retain contrast and was stable after 15 minutes. (From Kinlay S, Bhatt DL. Treatment of noncoronary obstructive vascular disease. In: *Braunwald Heart Disease*, ed 12. Elsevier; 2022:863.e3).

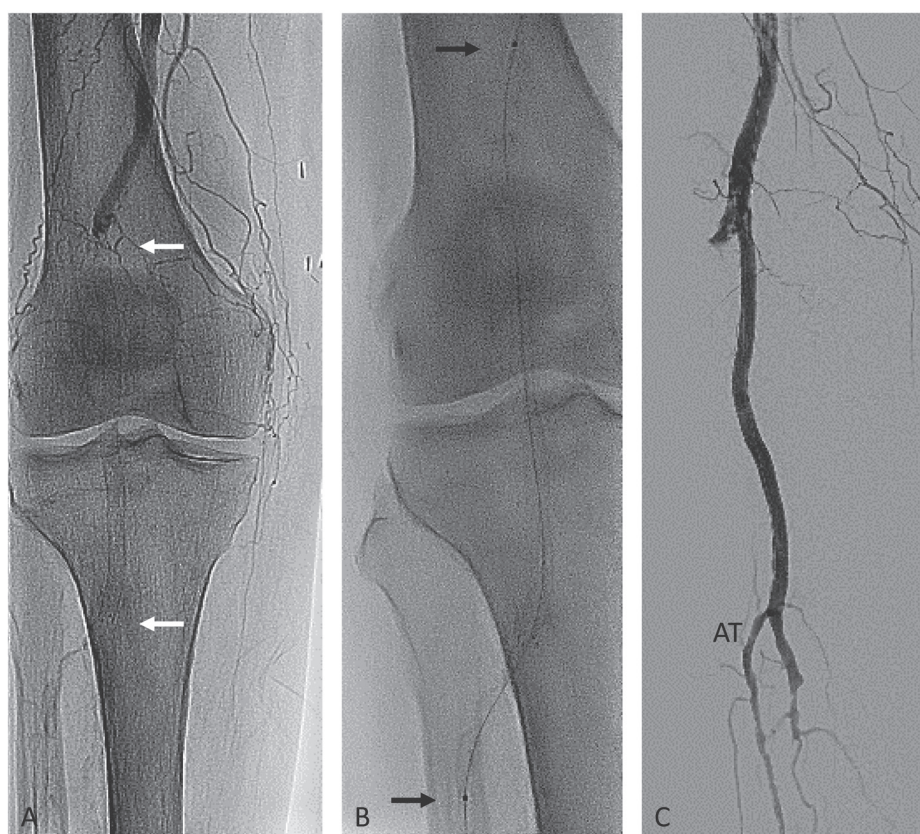


FIGURE 18.19 Catheter-based thrombolysis of a thrombosed and occluded right popliteal artery stent. **A**, Thrombosed right popliteal artery stent with white arrows indicating the proximal and distal edges of the stent. **B**, Multiholed infusion catheter placed with proximal and distal markers of the infusion segment indicated with arrows. **C**, Angiogram 24 hours later showing a patent popliteal stent and outflow into the anterior tibial artery (AT). (From Kinlay S, Bhatt DL. Treatment of noncoronary obstructive vascular disease. In: *Braunwald Heart Disease*, ed 12. Elsevier; 2022:862).

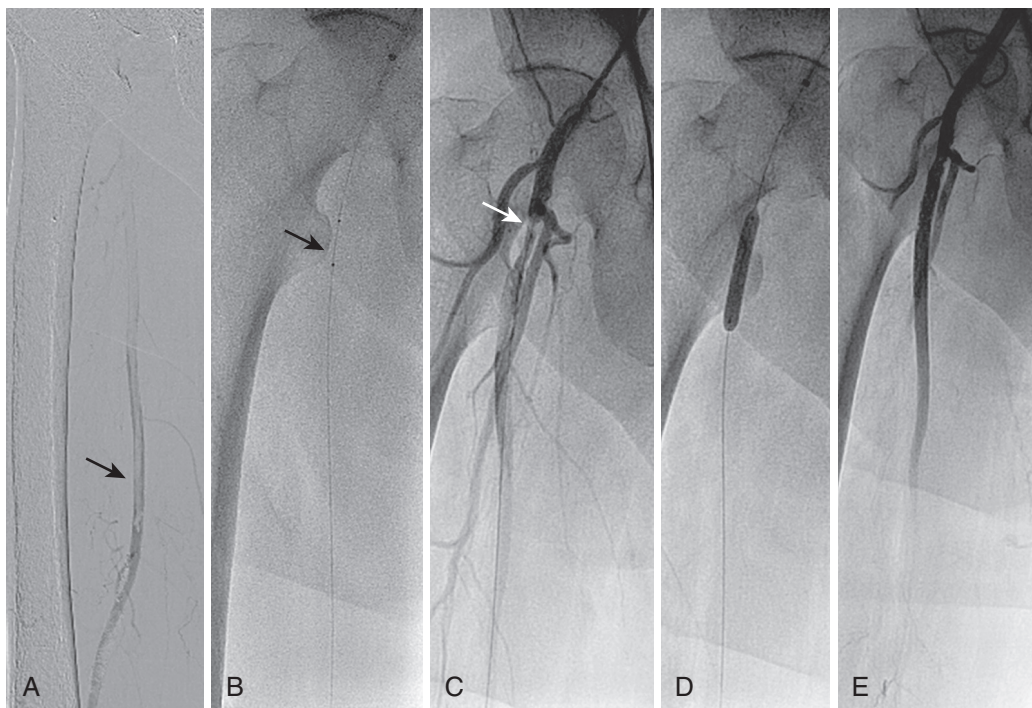


FIGURE 18.20 Thrombolysis using pulse-spray mechanical thrombolysis (same case as Figure 18.1). **A**, Late-phase angiogram showing a long filling defect in the superficial femoral artery consistent with in situ thrombus (arrow). **B**, Pulse-spray thrombolysis using a 4-Fr AngioJet catheter and 10 mg of recombinant tissue plasminogen activator over a 5.0-mm Spider X embolic protection device (arrow at the tip of the catheter). After 20 minutes, the catheter was switched to aspiration mode, and the thrombus slurry was removed with several aspiration runs. **C**, Residual stenosis at the origin of the superficial femoral artery (arrow). **D**, Balloon angioplasty of the residual lesion. **E**, Final result.

saline). The solution is left for 20 minutes, and then the AngioJet is converted to the usual aspiration setup and the solution and thrombus aspirated. The Jetstream is an atherectomy device that has an aspiration port that can be used to aspirate thrombus. Thrombolytic agents can be added to the saline perfusion to assist thrombectomy.

The Penumbra Indigo (Penumbra; https://www.access-data.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?start_search=1&Center=&Panel=&ProductCode=NRY&KNumber=&Applicant=PENUMBRA%2C%20INC%2E&DeviceName=&Type=&ThirdPartyReviewed=&ClinicalTrials=&Decision=&DecisionDateFrom=&DecisionDateTo=07%2F04%2F2017&IVDProducts=&Redact510K=&CombinationProducts=&ZNumber=&PAGENUM=25&sortcolumn=dn_desc) aspiration system uses a mechanical aspirator and a range of 3- to 8-Fr catheters to generate a greater suction than manual aspiration.

Catheter-based thrombolysis can effectively restore perfusion to an ischemic limb. However, if there is substantial ischemia, reperfusion syndrome can occur, with tissue swelling leading to limb ischemia from a compartment syndrome requiring urgent fasciotomy.³

Intravascular Imaging

Intravascular imaging can help keep equipment within the artery wall when crossing an occlusion, measure the diameter of an artery for device sizing, and assess any angiographic features that could represent dissections or other structural abnormalities. The two key imaging techniques

are intravascular ultrasonography (IVUS) and OCT. Although OCT has higher spatial resolution, its poor depth penetration compared with IVUS limits its usefulness in the large peripheral arteries.

Intravascular ultrasonography is coupled with one re-entry device to help locate the distal true lumen after dissecting through an occlusion (see Figure 18.8). It can also show whether a wire is within the artery or exiting an occluded artery (Figure 18.21) and help show the underlying anatomical defect—for example, a popliteal aneurysm in an occluded popliteal artery (see Figure 18.13).

INTERVENTIONS IN SPECIFIC ARTERIES

Aortoiliac Interventions

Successful aortic or iliac interventions often make a great difference to function and quality of life in patients with symptoms caused by PAD. Although an ipsilateral common femoral access is often used, many operators obtain additional access from the contralateral femoral artery or from the radial artery to improve visualization, particularly when treating a common iliac occlusion (see Figures 18.4 and 18.10). The external iliac artery dips into the pelvis from the common femoral artery and is the most common site of peripheral artery perforation by wires or balloon or stent expansion. Contralateral or arm access allows the operator to rapidly deploy a proximal iliac or aortic occluding balloon if intervention from the ipsilateral side leads to perforation.

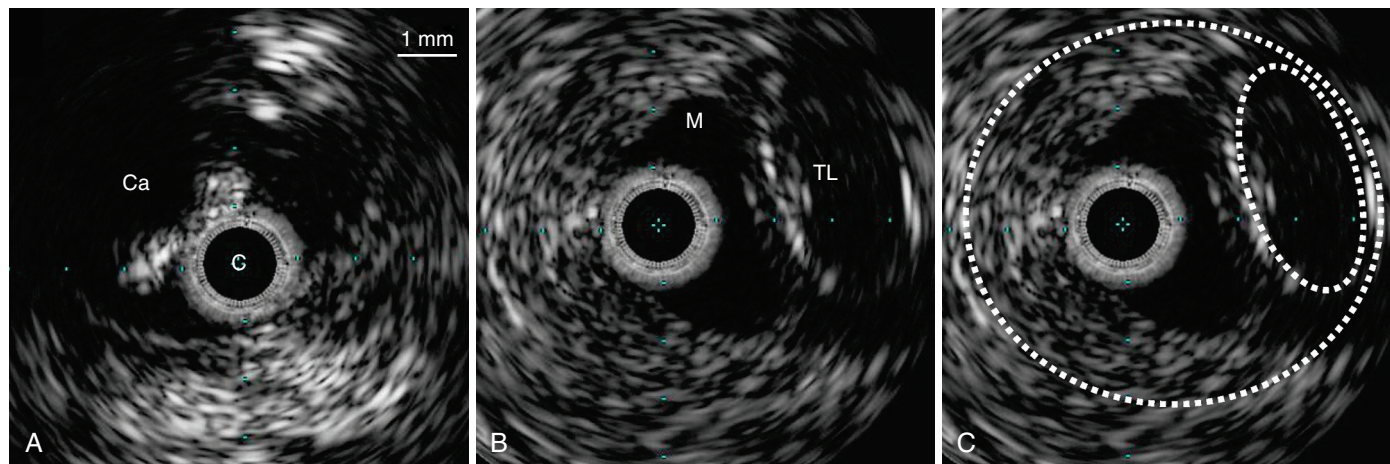


FIGURE 18.21 Intravascular ultrasound (IVUS) used to document the true lumen of a total superficial femoral artery (SFA) occlusion (see Figure 18.15D for the corresponding angiogram). **A**, IVUS in the lumen of the proximal SFA showing a calcified plaque (Ca) at 9 to 12 o'clock adjacent to the catheter (C) in the artery lumen. **B**, IVUS in an intramedial location (M) with the true lumen appearing as an *ellipse* to the right of the catheter. **C**, Same image as B showing the true lumen (*inner oval*) and the total vessel area bounded by the adventitia (*outer circle*).

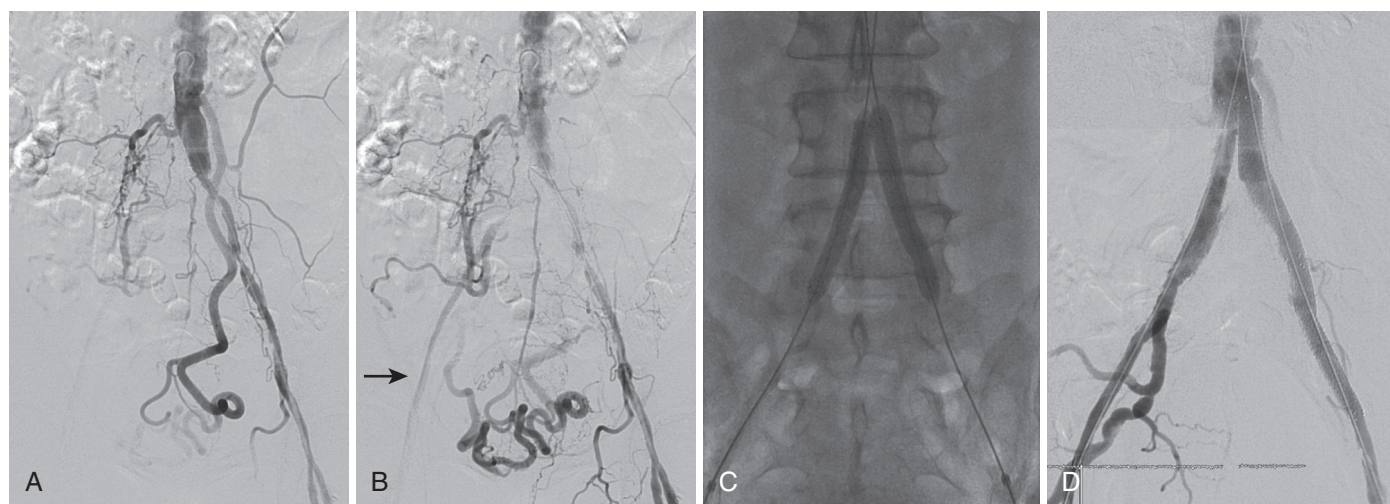


FIGURE 18.22 Aortoiliac intervention for an occluded right common iliac and serial stenoses in the left iliac arteries. **A**, Early phase angiogram showing occlusion of the right common iliac artery. **B**, Late phase angiogram showing patent right external iliac artery (arrow). **C**, Bilateral kissing balloon expandable stents in the common iliac arteries. **D**, Composite angiogram showing final result. (From Kinlay S, Bhatt DL. Treatment of noncoronary obstructive vascular disease. In: *Braunwald Heart Disease*, ed 10. Elsevier; 2015:1355).

Ipsilateral retrograde access from the common femoral artery with a 6-Fr sheath offers good support for crossing an iliac lesion (Figure 18.22). Use of a sheath with a radiopaque tip prevents inflating a balloon or stent within the tip of the sheath, particularly in lesions that are close to the sheath, such as the external iliac artery.

Although balloon angioplasty has acceptable results in these large arteries, iliac stenting commonly uses stents because of better long-term patency and prevention of recoil after balloon deflation. Balloon-expandable stents are less likely to move on deployment and offer greater radial strength than self-expanding stents. They are therefore favored by many operators, except in the distal external iliac artery because there may be some external compression as this artery ascends into the common femoral artery over the hip joint.

The origins of the common iliac arteries can be treated with “kissing stents” that create a higher carina. However,

this technique makes it very hard to use a contralateral approach if this is needed in the future. Landing proximal common iliac stents at the ostia preserves this access for future interventions (see Figure 18.22).

The durability of bare-metal iliac stents is excellent and similar to those of surgical revascularization, with greater than 80% patency at 5 years, although it is slightly less in cigarette smokers. The value of covered stents in preventing restenosis is uncertain, but they are often used for lesions at risk of perforation or major dissection (see earlier section on covered stents).

Superficial Femoral Artery

The superficial femoral artery is the most common peripheral artery leading to symptomatic PAD. The profunda femoral artery is rarely affected by obstructive atherosclerosis but usually provides an important source of

collaterals when the superficial femoral artery is diseased. Thus, endovascular interventions try to avoid the common femoral artery or jailing the profunda artery because restenosis or occlusion of these arteries can lead to ALI and limb loss.

The contralateral femoral access is the principal approach for disease involving the proximal superficial femoral artery because there is not enough room to securely place a sheath from an ipsilateral antegrade common femoral approach (see [Figures 18.15](#) and [18.20](#)). However, the radial approach with dedicated equipment may become more common, particularly if adjunctive devices and drug-coated devices are developed with long shafts to reach the distal superficial femoral artery.

The contralateral iliac artery is engaged selectively with a mammary catheter or nonselectively with an Omni-flush or pigtail catheter. An angled 0.035-inch hydrophilic wire is used to select the contralateral iliac system and deliver the catheter into the contralateral common femoral artery. The wire is exchanged for a stiff J-wire, and the catheter and femoral sheath are exchanged for a 45- to 55-cm sheath (e.g., Balkin or Ansel). The superficial femoral artery lesion is crossed with any type of wire. For stenosis, a highly torquable coronary 0.014-inch wire may be suitable initially and can be exchanged for an 0.018- or 0.035-inch wire for larger balloon angioplasty or stenting. Occlusions can be crossed with stiff 0.014-inch wires or hydrophilic 0.018-, 0.025-, or 0.035-inch wires by leading with the wire tip or using a loop induced in the wire at the transition of the soft and stiff parts of the wire. This technique often dissects through the media and even close to the adventitia (see [Figure 18.21](#)), and both techniques can lead to wire perforation of the artery. Successful crossing of an occlusion can be confirmed by angiography in one or two angulations or injection of contrast through a catheter or balloon delivered over the wire into the distal true lumen (see [Figure 18.15E](#)).

Retrograde access from the distal superficial femoral artery, popliteal artery, or a tibial artery with a small 4- or 5-Fr sheath can successfully cross a CTO. In this case, a retrograde wire can be snared from a sheath placed contralaterally in the common femoral artery and the wire tip externalized. This “dental floss” technique is also used in the iliac artery ([Figure 18.23](#) and [Video 18.1](#)) and increases the support to deliver balloons across the occlusion for treatment. After successful intervention, the distal artery sheath is removed after anticoagulation has worn off and hemostasis achieved with manual compression.

Balloon angioplasty is the most common intervention using balloons with diameters of 5 to 6 mm for the superficial femoral artery and 4 to 5 mm for the above-knee popliteal artery (see [Figure 18.9](#)). Self-expanding stents are reserved for long lesions (>100–150 mm) or flow-limiting dissections when there is evidence they lead to greater patency than balloon treatment alone (see [Figure 18.11](#)). Self-expanding stents are usually selected as a diameter 1 mm greater than the reference lumen of the artery to ensure they appose the artery wall. An undersized self-expanding stent cannot be made larger by bigger balloon inflation because the nitinol memory leads it to recoil to the predetermined size. It is often difficult to place long

self-expanding stents because the most proximal end of the stent may shrink or extend longitudinally compared with the undeployed position. Often a short self-expanding stent is needed to treat the lesion back to the superficial femoral artery origin. In some cases, it may be better to treat a short proximal length of the ostium of the superficial femoral artery by balloon angioplasty alone rather than risk jailing the profunda artery in an attempt to cover the ostium of the superficial femoral artery. This may be a more viable alternative with the advent of drug-eluting balloons.

Very long femoral artery stenting (>200 mm) with bare-metal stents is associated with relatively high rates of restenosis ($\leq 40\%$ – 50% over 2.5 years). However, drug-eluting self-expanding stents reduce this risk by 30% to 50%.^{14,15} Restenosis can be treated with repeat balloon angioplasty ([Figure 18.24](#)), with long segments treated with drug-coated balloons²⁸ to improve overall patency and justifying close outpatient surveillance in both claudication and CLI.

Atherectomy may be used for lesions resistant to angioplasty (e.g., heavily calcified lesions) (see [Figures 18.14](#) and [18.15](#)), but its value beyond balloon angioplasty for most lesions is uncertain, with increased risk of embolization and perforation. Embolic protection devices may be helpful in preventing distal embolization.

Popliteal Artery

The popliteal artery starts at Hunter’s canal above the knee and ends at the junction of the anterior tibial and peroneal-tibial trunk arteries below the knee. This artery is subject to a great range of movement with walking and bending of the knee. Most of the flexion of the popliteal artery occurs below the upper margin of the patella to the lower margin of the tibial epiphyseal plate (see [Figure 18.13L](#)). Therefore, most operators try to avoid stenting this region unless they are treating a patient with CLTI/CLI and have a poor balloon angioplasty result (flow-limiting dissection). Specific woven nitinol stents may be more durable than other self-expanding stents in the popliteal artery over the knee joint but have less radial strength and require adequate arterial dilation before deployment.²⁹ Occlusion of the popliteal artery can be treated with atherectomy and balloon angioplasty and increasingly drug-coated balloon treatment to avoid stenting (see [Figure 18.14](#)), but it is important to recognize thrombosis of a popliteal aneurysm as a cause of occlusion (see [Figure 18.13](#)). This latter condition is associated with catastrophic embolization and loss of the tibial arteries, leading to major amputation, and is best treated by surgical ligation and bypass. Although covered stents are used to treat popliteal aneurysms, their durability compared with surgery is uncertain. Covered stents can exclude important geniculate collaterals, and if they subsequently occlude, this can lead to an acute limb syndrome caused by loss of the main artery and collaterals (see [Figure 18.13L](#)).

Tibial Arteries

Disease of the tibial arteries rarely causes claudication, and most operators only intervene on these arteries for CLTI/CLI. Reperfusion syndrome (e.g., after revascularization of ALI) or perforation of a tibial artery can also lead to

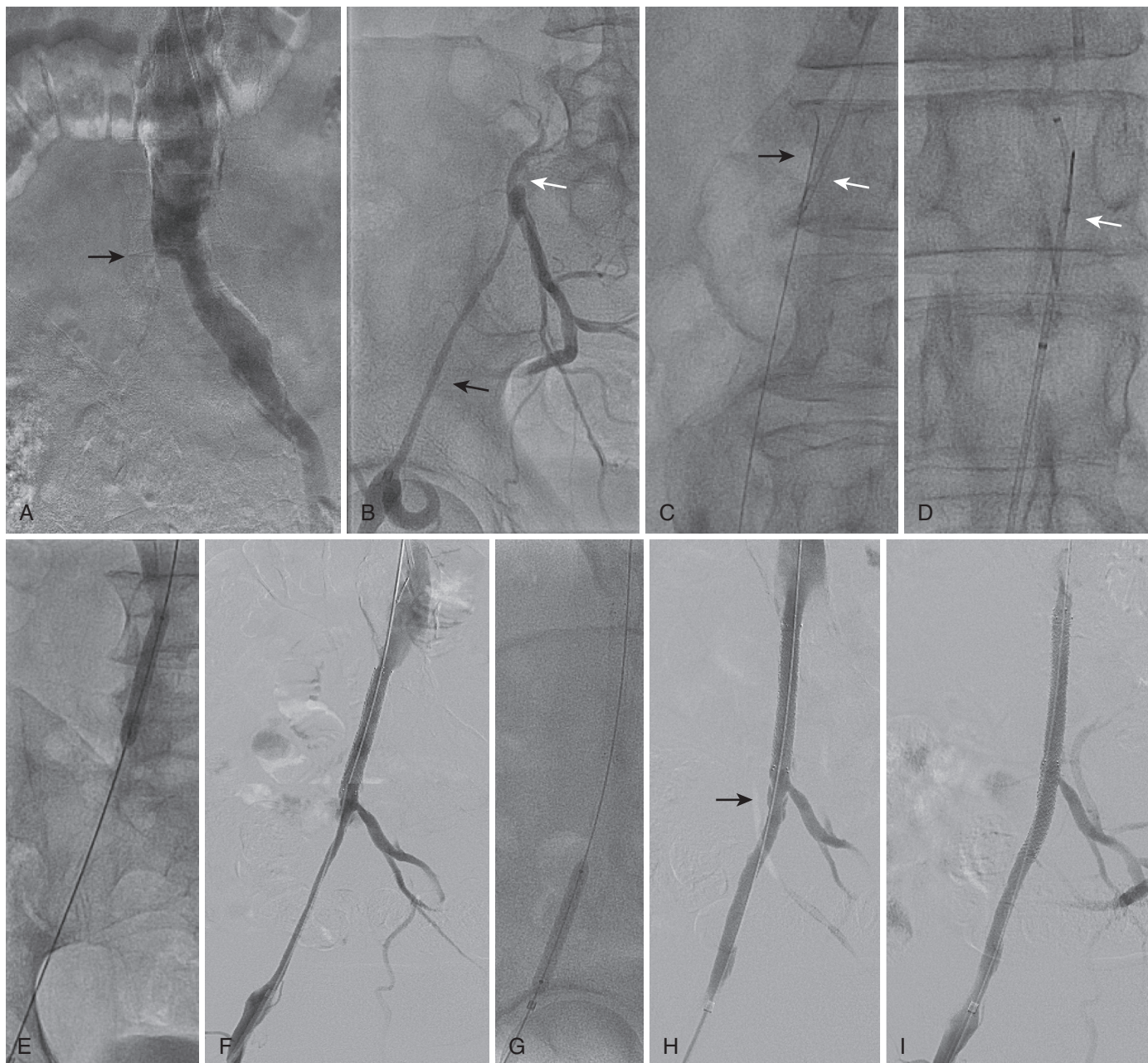


FIGURE 18.23 Antegrade and retrograde approach to an occluded right common iliac artery. **A**, Angiogram using a multipurpose catheter from the right brachial artery and positioned at the aortic bifurcation and showing an occluded right iliac artery (arrow). **B**, Angiogram from a sheath placed in the right common femoral artery showing a long stenosis of the right external iliac artery (black arrow), a patent internal iliac artery, and the distal occlusion cap of the common iliac artery (white arrow). **C**, A 0.025-inch hydrophilic wire is advanced retrograde through the occluded common iliac artery (black arrow) and adjacent to the multipurpose catheter (white arrow). **D**, The wire and a 0.035-inch support catheter are snared from above and pulled through the occlusion. **E**, The common iliac artery is dilated and stented from below using an 8.0- × 60-mm balloon-expandable stent. **F**, Angiogram showing a patent right common iliac artery and stenosis in the external iliac artery. **G**, Several dilations of the external iliac artery and common femoral artery made with low-medium pressure dilations of a 7.0-mm balloon. **H**, Dissection of the ostium of the external iliac artery (arrow). **I**, After stenting, the proximal external iliac artery showing a patent right common iliac, internal iliac, external iliac, and common femoral arteries.

catastrophic compartment syndrome with loss of muscle and need for amputation. An ipsilateral antegrade common femoral artery access allows insertion of balloons into the foot and provides greater support compared with a contralateral femoral approach (see [Figures 18.4](#) and [18.7](#)). Because the tibial arteries are similar in size to coronary arteries, many of the coronary 0.014-inch wires, catheters, and balloons can be used to cross these lesions. Use of long sheaths or a multipurpose coronary intervention guide

placed in the popliteal artery increases support and leads to better angiograms with reduced use of contrast. This technique can be combined with retrograde pedal access using noninvasive ultrasound and micropuncture access at the foot or ankle to help cross a popliteal or tibial artery occlusion, snare the wire from above, and then provide a solid rail to advance balloons through the occlusion (see [Figure 18.6](#)). However, if this approach is unsuccessful, the pedal access site may become a nonhealing ulcer.

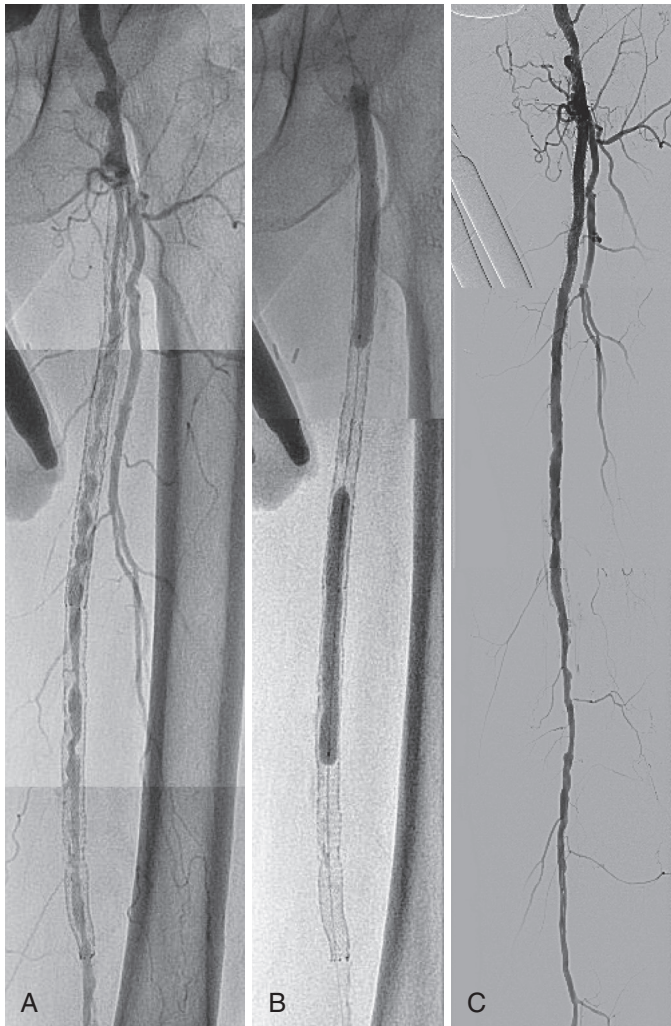


FIGURE 18.24 Balloon angioplasty of diffuse restenosis of a long superficial femoral artery stent. **A**, Diffuse in-stent restenosis. **B**, Collage of different angiograms showing balloon dilations with a 6.0- × 80-mm balloon along the length of the stents. **C**, Final angiogram showing a widely patent stent.

Long 0.014-inch compatible peripheral balloons of 80- to 150-mm balloon lengths are often stiffer and prevent the need for multiple overlapping inflations with short coronary balloons. Although restenosis is more common after treating long, diffuse, and often calcified tibial arteries, increasing perfusion may allow wound and tissue healing before restenosis. In the event of poor wound healing due to restenosis, repeat angioplasty is often successful. Drug-eluting balloons may have an important impact in preserving tibial artery patency and increasing wound healing rates in CLTI/CLI, although there is less supporting evidence for this location compared with femoral-popliteal disease.

Angiosome-directed revascularization refers to revascularization of a tibial artery that supplies the area of a non-healing ulcer or gangrene (Figure 18.25). The value of angiosome-directed revascularization versus restoring any straight flow to the foot is debated. In observational studies, wound healing was better and amputation rates lower with angiosome-directed rather than nonangiosome tibial revascularization.⁶ However, these observations may be

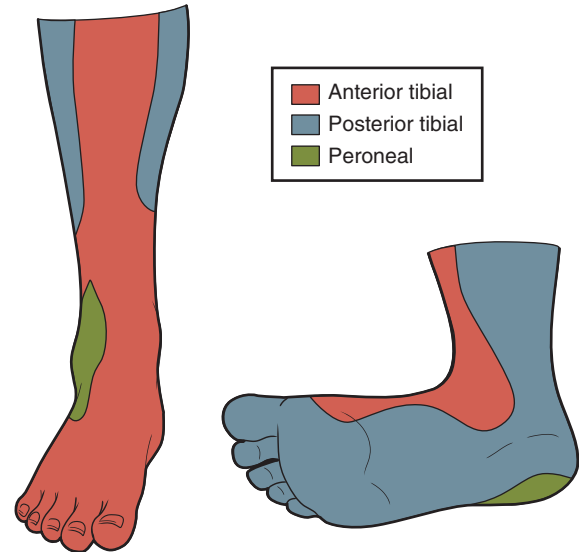


FIGURE 18.25 Angiosome distributions showing regions supplied by the three below-knee arteries. (From Kinlay S. Management of critical limb ischemia. *Circ Cardiovasc Interv.* 2016;9:e001946.)

confounded because indirect revascularization may be a marker of more complex tibial disease and poorer limb outcomes.⁶

Managing ulcers and gangrene in CLI requires close follow-up to debride dead tissue. Gangrenous toes can be left dry until they mummify and autoamputate or can be surgically amputated after viable and devitalized tissue are clearly demarcated. Infected or wet gangrene may lead to osteomyelitis and requires surgical amputation. These complexities mandate a team approach to care that includes specialists in wound care, podiatry, surgery, and prosthetics.

Venous and Prosthetic Graft Interventions

Bypass grafts can renarrow at the proximal and distal anastomoses with native arteries or in the body of the graft. Patients with vein graft stenosis can be successfully treated with balloon angioplasty and stents used as bail-out for flow-limiting dissections of recoil. If an anastomosis lesion occurs soon after the initial bypass graft, the surgeon may prefer surgical revision to endovascular treatment. Although short-term outcomes after endovascular intervention are similar to those for open surgical revision, the differences in long-term outcomes are uncertain. Prosthetic graft disease is more difficult to treat by endovascular methods because positive remodeling of the prosthetic graft is not possible. Balloon angioplasty may remodel the plaque, displacing it longitudinally, but long-term results are unknown. Atherectomy could potentially remove plaque in prosthetic grafts, but any perforation is likely to lead to a rapid blood loss in part because there is no vasoconstriction reflex in prosthetic grafts (this is also likely in diseased vein grafts). Therefore, covered stenting may be required in this case. Patients with prosthetic graft disease are probably best treated by surgical revision. However, endovascular approaches may be required when a patient lacks vein conduit or the risks of repeat bypass are

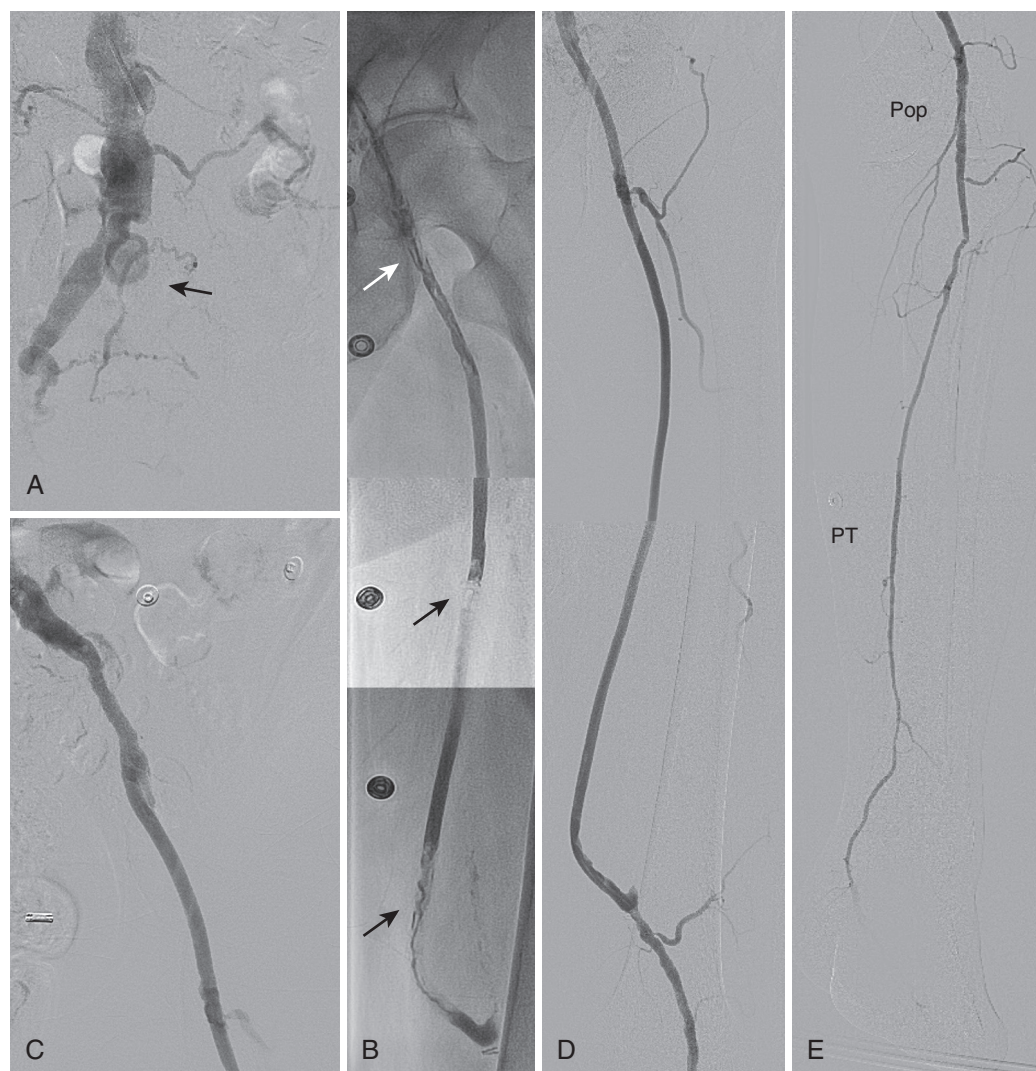


FIGURE 18.26 Thrombolysis of a thrombosed femoral to popliteal prosthetic graft. **A**, The proximal left common iliac artery is occluded with thrombus (arrow). **B**, The thrombus extends through a left external iliac stent with filling defects in the proximal (white arrow) mid and distal graft (black arrows) and no distal outflow from the graft. **C**, Twenty-four hours after catheter-based thrombolysis, the left common and external iliac arteries are patent. **D**, Similarly, graft patency is restored, and there is distal outflow into the native popliteal artery. **E**, Distal runoff below the knee through the distal popliteal artery and posterior tibial artery. Pop, Popliteal artery; PT, posterior tibial artery.

prohibitively high because of comorbidities or extensive fibrosis in the surgical field.

Catheter-based thrombolysis can successfully treat a thrombosed prosthetic graft (Figure 18.26 and Video 18.6). Long-term patency is higher if a correctable causal lesion is treated (e.g., a graft anastomosis stenosis).^{1,2}

CONCLUSIONS

Advances in percutaneous intervention techniques and equipment have increased the options and success of treating occlusive disease of arteries, veins, and bypass grafts of the lower extremities. The interventionalist needs to be aware of vasculitis, entrapment, and other conditions that may respond better to treatments other than revascularization. Initiating atherosclerosis risk factor control, healthy lifestyles, and physical activity are important to improve long-term outcomes in patients. When

percutaneous revascularization is appropriate, planning the procedure to optimize success includes considering vascular access, the use of specialized equipment, and ingenuity to tackle complex lesions such as CTOs. Backup plans, knowing when to stop a procedure, and an adequate inventory (e.g., covered stents for perforation) are part of forward planning to avoid or treat complications.

REFERENCES

1. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J*. 2018;39:763-816.
2. Gornik HL, et al. ACC/AHA PAD Guidelines *** PLACEHOLDER ***. *JACC or Circulation*. 2022.
3. McNally MM, Univers J. Acute limb ischemia. *Surg Clin North Am*. 2018;98:1081-1096.

4. Ebben HP, Jongkind V, Wisselink W, Hoksbergen AWJ, Yeung KK. Catheter directed thrombolysis protocols for peripheral arterial occlusions: a systematic review. *Eur J Vasc Endovasc Surg*. 2019;57:667-675.
5. Robertson L, McBride O, Burdess A. Pharmacomechanical thrombectomy for iliofemoral deep vein thrombosis. *Cochrane Database Syst Rev*. 2016;11:CD011536.
6. Kinlay S. Management of critical limb ischemia. *Circ Cardiovasc Interv*. 2016;9:e001946.
7. Kullo IJ, Rooke TW. Clinical practice. Peripheral artery disease. *N Engl J Med*. 2016;374:861-871.
8. Polonsky TS, McDermott MM. Lower extremity peripheral artery disease without chronic limb-threatening ischemia: a review. *JAMA*. 2021;325:2188-2198.
9. Aday AW, Kinlay S, Gerhard-Herman MD. Comparison of different exercise ankle pressure indices in the diagnosis of peripheral artery disease. *Vasc Med*. 2018;23:541-548.
10. Kim ES, Sharma AM, Scissons R, et al. Interpretation of peripheral arterial and venous Doppler waveforms: a consensus statement from the Society for Vascular Medicine and Society for Vascular Ultrasound. *Vasc Med*. 2020;25:484-506.
11. Banerjee S, Jeon-Slaughter H, Tsai S, et al. Comparative assessment of procedure cost and outcomes between guidewire and crossing device strategies to cross peripheral artery chronic total occlusions. *JACC Cardiovasc Interv*. 2016;9:2243-2252.
12. Weissler EH, Gutierrez JA, Patel MR, Swaminathan RV. Successful peripheral vascular intervention in patients with high-risk comorbidities or lesion characteristics. *Curr Cardiol Rep*. 2021;23:32.
13. Candy N, Ng E, Velu R. Paclitaxel-coated balloon reduces target lesion revascularization compared with standard balloon angioplasty. *J Vasc Surg*. 2017;65:558-570.e10.
14. Dake MD, Ansel GM, Jaff MR, et al. Durable clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX randomized trial. *Circulation*. 2016;133:1472-1483; discussion 1483.
15. Gray WA, Keirse K, Soga Y, et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. *Lancet*. 2018;392:1541-1551.
16. Muller-Hulsbeck S, Keirse K, Zeller T, Schroe H, Diaz-Cartelle J. Long-term results from the majestic trial of the eluvia paclitaxel-eluting stent for femoropopliteal treatment: 3-year follow-up. *Cardiovasc Interv Radiol*. 2017;40:1832-1838.
17. Bosiers M, Setacci C, De Donato G, et al. ZILVERPASS study: ZILVER PTX stent vs bypass surgery in femoropopliteal lesions. *J Endovasc Ther*. 2020;27:287-295.
18. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2018;7:e011245.
19. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Paraskevopoulos I, Karnabatidis D. Risk of death and amputation with use of paclitaxel-coated balloons in the infrapopliteal arteries for treatment of critical limb ischemia: a systematic review and meta-analysis of randomized controlled trials. *J Vasc Interv Radiol*. 2020;31:202-212.
20. Bittl JA, He Y, Baber U, Feldman RL, von Mering GO, Kaul S. Bayes factor meta-analysis of the mortality claim for peripheral paclitaxel-eluting devices. *JACC Cardiovasc Interv*. 2019;12:2528-2537.
21. Gray WA, Jaff MR, Parikh SA, et al. Mortality assessment of paclitaxel-coated balloons: patient-level meta-analysis of the ILLUMENATE clinical program at 3 years. *Circulation*. 2019;140:1145-1155.
22. Schneider PA, Laird JR, Doros G, et al. Mortality not correlated with paclitaxel exposure: an independent patient-level meta-analysis of a drug-coated balloon. *J Am Coll Cardiol*. 2019;73:2550-2563.
23. Secemsky EA, Kundi H, Weinberg I, et al. Association of survival with femoropopliteal artery revascularization with drug-coated devices. *JAMA Cardiol*. 2019;4:332-340.
24. Behrendt CA, Sedrakyan A, Peters F, et al. Editor's choice—long term survival after femoropopliteal artery revascularisation with paclitaxel coated devices: a propensity score matched cohort analysis. *Eur J Vasc Endovasc Surg*. 2020;59:587-596.
25. Scheller B, Vukadinovic D, Jeger R, et al. Survival after coronary revascularization with paclitaxel-coated balloons. *J Am Coll Cardiol*. 2020;75:1017-1028.
26. Kansal A, Long CA, Patel MR, Jones WS. Endovascular treatment of femoropopliteal lesions. *Clin Cardiol*. 2019;42:175-183.
27. Madhavan MV, Shahim B, Mena-Hurtado C, Garcia L, Crowley A, Parikh SA. Efficacy and safety of intravascular lithotripsy for the treatment of peripheral arterial disease: an individual patient-level pooled data analysis. *Catheter Cardiovasc Interv*. 2020;95:959-968.
28. Anantha-Narayanan M, Love K, Nagpal S, Sheikh AB, Regan CJ, Mena-Hurtado C. Safety and efficacy of paclitaxel drug-coated balloon in femoropopliteal in-stent restenosis. *Expert Rev Med Devices*. 2020;17:533-539.
29. Garcia LA, Rosenfield KR, Metzger CD, et al. SUPERB final 3-year outcomes using interwoven nitinol biomimetic Supera stent. *Catheter Cardiovasc Interv*. 2017;89:1259-1267.



19

Upper Extremity Intervention

AMJAD T. ALMAHAMEED

INTRODUCTION, 362

DIAGNOSIS AND CLINICAL SYNDROMES, 362

TREATMENT, 363

Surgical Revascularization, 364
Endovascular Therapy, 364

CONCLUSIONS, 368

INTRODUCTION

Atherosclerotic upper extremity obstructive disease is predominantly secondary to subclavian or innominate artery stenosis (SAS or IAS). The diagnosis is usually suspected when a significant (often ≥ 15 mm Hg) systolic brachial blood pressure discrepancy (BBPD) is detected between the two arms.^{1,2} Applying this threshold, the prevalence of SAS in the general population is estimated at approximately 2% and increases with advancing age. In a high-risk population with known or suspected vascular disease, including individuals referred for coronary artery bypass surgery, the prevalence is estimated at about 7%.^{1,2} Involvement of the left subclavian artery (L-SCA) is three to four times more common than the right brachiocephalic and subclavian arteries.^{3,5} This may be explained by increased flow turbulence in the L-SCA because of its acute angle of origin. Moreover, one-third of the stenotic lesions on the right side are found in the innominate trunk proximal to the subclavian origin.^{6,7}

The presence of SAS correlates well with known atherosclerotic risk factors and is a strong indicator of the presence of peripheral artery disease (PAD), defined as an ankle brachial index of 0.90 or less.^{2,8} The incidence is much higher in patients with symptomatic PAD. In one study of 48 participants with PAD who underwent aortic arch angiography, 19% had more than 50% stenosis of at least one brachiocephalic artery.⁹ Furthermore, SAS predicts total and cardiovascular mortality (independent of both risk factors and existent cardiac disease at baseline) and all-cause mortality.^{8,10} Overall, it is estimated that SAS is present in 11.5% of patients with known PAD. Therefore, we routinely recommend bilateral blood pressure measurements in high-risk patients.^{2,11}

Nonatherosclerotic conditions that can result in BBPD and SAS include Takayasu's arteritis,¹² giant cell arteritis,¹³ coarctation of the aorta,¹⁴ thoracic outlet syndrome causing compression from an overlying rib,¹⁵ radiation-induced vascular disease,¹⁶ and rarely, fibromuscular dysplasia (FMD),¹⁷ arterial thrombosis (Figure 19.1), and neurofibromatosis.¹⁸ Therefore, routine evaluation for these disorders is not warranted. FMD is more likely to affect small- and medium-sized arteries, notably the brachial artery, and can occasionally lead to upper extremity ischemia and bilateral pulse discrepancy. Importantly, the presence of a BBPD with associated acute chest pain should alert the clinician for the possibility of aortic dissection.



FIGURE 19.1 Thrombus noted in the proximal left subclavian artery. This patient presented with left hand ischemia.

DIAGNOSIS AND CLINICAL SYNDROMES

Isolated SAS rarely leads to symptoms, perhaps because of the lower muscular mass it supplies (compared with that supplied by the lower extremity inflow arteries) and the high degree of collateralization. Symptoms related to vertebralbasilar insufficiency (also referred to as vertebral subclavian steal syndrome [vSSS]) remain uncommon with isolated SAS and most likely occur when multiple craniocervical arteries are stenotic or occluded.¹⁹ The clinical manifestations of SAS are listed in Table 19.1. Common neurologic symptoms of vSSS include dizziness, vertigo, visual disturbance, dysphagia, dysarthria, facial sensory deficits, and fainting, typically triggered by ipsilateral upper extremity exertion.

With regard to vertebral subclavian steal syndrome, Lord et al.¹⁹ showed that the discontinuity of the circle of Willis caused by the vertebral–vertebral shunt (from the patent vertebral artery [VA] to the occluded one, across the circle of Willis) is responsible for symptoms experienced during

TABLE 19.1 Clinical Manifestations of Subclavian Artery Stenosis

Arm ischemia	Arm claudication, muscle fatigue, hand or finger pain, paresthesias, coldness in the arm, Raynaud's phenomenon, distal embolization and its sequelae of tissue loss and necrosis
Vertebral subclavian steal syndrome	Symptoms of vertebrobasilar insufficiency: paroxysmal vertigo, drop attacks, ataxia, diplopia, motor dysphagia, dysarthria, and facial motor deficits; typically seen with concurrent vertebral and carotid disease
Coronary subclavian steal syndrome	Angina pectoris, refractory unstable angina, MI, heart failure in patients with LIMA (or, rarely, RIMA) graft
CVA or paralysis after TEVAR with coverage of the L-SCA ²⁰	Risk estimated at 4.7% vs 2.7% in patients without L-SCA coverage; preemptive revascularization offers no protection against CVA when coverage is applied
Lower extremity claudication after AXF bypass	Seen in patients with history of ipsilateral axillary-femoral bypass.
Arm ischemia	Arm claudication, muscle fatigue, hand or finger pain, paresthesias, Raynaud's phenomenon, distal embolization, tissue loss, and necrosis
Carotid subclavian steal syndrome	Rare except in proximal innominate artery stenosis

AXF, axillary-femoral bypass graft; CVA, cerebrovascular accident; LIMA, left internal mammary artery; L-SCA, left subclavian artery; MI, myocardial infarction; RIMA, right internal mammary artery; TEVAR, thoracic endovascular aortic repair.

repetitive use of the affected upper extremity. Occasionally, the blood is routed from the anterior circulation through the descending cervical branches of the ipsilateral external carotid artery, providing collateral pathways to the occluded subclavian artery. In the later cases, symptoms of anterior circulation ischemia, such as transient hemiparesis, speech disturbances, and sensory loss, may be reported.²⁰ On the other hand, ischemic syndromes attributable to the anterior circulation are more common in symptomatic patients presenting with occlusive lesions of the right innominate trunk. Fifty percent of such patients express anterior ischemia, 40% present with posterior symptoms, and up to 10% manifest global (anterior and posterior) symptoms.²¹

The Javid test is a highly reliable clinical maneuver in demonstrating flow reversal via the circle of Willis. In this test, the examiner compresses the ipsilateral carotid artery, thereby decreasing intracranial pressure and flow and abolishing retrograde flow into the arm. This leads to an abrupt change in the quality of the ipsilateral radial pulse.²²

Acute symptoms of arm or cerebral ischemia usually result from acute injury to the subclavian artery, as seen with sharp and blunt trauma, inadvertent misplacement of a large venous catheter into an SCA,²³⁻²⁶ and coverage by a stent graft during thoracic endovascular aortic repair (TEVAR).²⁷

Most cases of SAS are asymptomatic and diagnosed either incidentally on imaging studies or during routine physical examination. In addition to BBPD 15 mm Hg or greater, careful physical examination can yield absent or markedly diminished distal pulses and a systolic supraclavicular bruit. The bruit is best auscultated by lightly applying the stethoscope bell in each supraclavicular fossa while the patient sits looking forward with the shoulders relaxed and hands resting on the lap. After it is detected, firm compression of the patient's ipsilateral radial artery decreases the SCA outflow and should shorten or obliterate the bruit. Arm exercises that can be carefully performed in the office (with the patient in a supine position to avoid provoking syncope) will induce peripheral vasodilation, thus augmenting the SCA outflow, which increases the turbulence across the stenotic lesion, rendering the bruit louder and longer.

Upper extremity claudication can manifest as muscle cramping or a fatigued arm with upper extremity physical activity (combing the hair, brushing the teeth) and rarely digital ischemia presenting as discoloration and or ulceration usually caused by distal atherosclerotic or thrombotic emboli.

Duplex ultrasonography (DUS) with color flow is the diagnostic first test of choice. This modality provides excellent information of the lesion, identifies disease in the rest of the aortic arch vessels, and adequately assesses flow direction in the VA. After the diagnosis is made and the symptoms are considered significant enough to warrant intervention, we routinely obtain computed tomography angiography (CTA) or magnetic resonance angiography (MRA) to confirm the diagnosis, exclude proximal VA stenosis or occlusion (difficult to visualize by DUS and when present can manifest as retrograde vertebral flow, mimicking vSSS), and clearly define the anatomic relationships between the SCA lesion, the aortic arch (because ostial lesions represent an extension of atherosclerosis arising in the aortic arch), and the origins of the ipsilateral vertebral and internal mammary arteries. This information can be very useful in planning the treatment modality. Angiography is reserved for patients who were determined to undergo endovascular therapy.

We recommend all patients referred to coronary artery bypass grafting (CABG) with BBPD 15 mm Hg or greater or a history of a nonatherosclerotic condition that is known to be associated with SAS (see earlier discussion) and those with known vascular disease to undergo screening for SAS before their open-heart surgery. This can be done in the outpatient setting by DUS or angiography during the index cardiac catheterization procedure.

TREATMENT

Patients with asymptomatic SAS are treated medically by applying global cardiovascular risk reduction strategies, including smoking cessation and antiplatelet therapy and achieving target blood pressure, glucose, and cholesterol. The goal of therapy in asymptomatic patients is to stabilize

the systemic atherosclerotic process and prevent disease progression and improve procedural outcomes. Currently, the evidence for revascularization of asymptomatic patients with hemodynamically significant SAS is lacking.²⁸ Patients who present with disabling symptoms of upper extremity ischemia, vSSS, scheduled to undergo CABG for severe coronary artery disease using ipsilateral left internal mammary artery (LIMA) (or already had ipsilateral LIMA grafted with evidence of coronary subclavian steal syndrome), need (or already have) an arteriovenous fistula for hemodialysis purposes, and when an axillofemoral graft is being considered are deemed appropriate for SAS revascularization. A reasonable argument is also made to revascularize bilateral upper extremity disease to allow for blood pressure monitoring and offer an access site for future invasive cardiac and vascular procedures.

Currently, more than 90% of patients undergoing subclavian artery revascularization are symptomatic.²⁹ Indications for revascularization procedures include the presence of one or more of the clinical syndromes outlined in Table 19.1.

Surgical Revascularization

Although surgical revascularization procedures have been employed since the 1950s, in most cases of SAS endovascular therapy is considered the modality of choice in contemporary practice.

Early surgical procedures used direct revascularization via transthoracic approach and were associated with significant morbidity and mortality.²⁹⁻³³ Anatomic revascularization procedures include endarterectomy and bypass grafts. These are technically demanding and associated with relatively high periprocedural complications. The evolution of extraanatomic cervical repair techniques improved surgical outcomes significantly.³² Therefore, extraanatomic revascularization procedures have been used and include carotid-subclavian transposition, carotid-subclavian bypass, axillo-axillary bypass, subclavian-subclavian bypass, and carotid-contralateral subclavian bypass (Figure 19.2).^{32,33} Hybrid procedures are generally reserved for aneurysmal disease when the stent graft (TEVAR) is extended to cover the subclavian artery. An open extraanatomic bypass is performed before deploying the graft. Of note, although this strategy may reduce the risk of spinal cord ischemia, it offers no protection against it, as demonstrated by Cooper et al.³⁴

A recent report by Aziz et al.³³ elegantly reviewed the English literature and reported the outcomes of the different endovascular and open surgical treatment modalities of the brachiocephalic arteries (Table 19.2).³³ Their findings verified the remarkable improvement in surgical outcomes compared with the 22% mortality rate described in early experiences 50 years ago.^{30,31,34,35} Subclavian-carotid artery transposition appears to have the greatest long-term patency for proximal subclavian artery occlusive disease (100% at 10 years), whereas axillo-axillary artery bypass surgery has the lowest patency rates, ranging from 88% to 89%.^{36,37}

Endovascular Therapy

The combination of recent advancements in endovascular techniques, along with the technical challenges of surgical

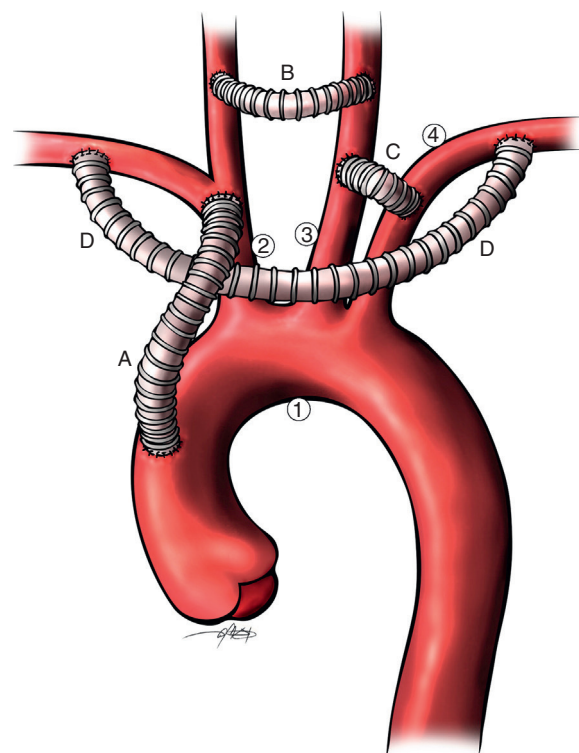


FIGURE 19.2 Illustration of brachiocephalic arteries and treatment strategies for revascularization. 1, Aortic arch; 2, innominate artery; 3, left common carotid artery; 4, left subclavian artery; A, aortoinnominate bypass; B, carotid-carotid bypass; C, left subclavian-carotid bypass; D, subclavian-subclavian/axillo-axillary bypass. (From Aziz F, Gravett MH, Comerota AJ. Endovascular and open surgical treatment of brachiocephalic arteries. *Ann Vasc Surg.* 2011;25:569-581.)

procedures and their associated serious complications (e.g., phrenic, vagus, and recurrent laryngeal nerve palsies; thoracic duct injuries; Horner's syndrome; and cerebral ischemia imposed by the need for proximal and distal cross clamping), made surgical revascularization progressively less popular.³⁸ Since its introduction in 1980 by Bachman and Kim,³⁹ percutaneous transluminal angioplasty became the treatment of choice for SAS and IAS. Endovascular therapy of completely occluded subclavian and innominate arteries was first reported in 1993 by Mathias et al.⁴⁰

Interventional Technique

After the decision to proceed with endovascular revascularization is made, a careful review of noninvasive studies (CTA or MRA) is critical for procedure planning. The anatomic relationships among the diseased segment, aortic arch, and other craniocervical arteries (carotid, VA, and IMA in the case of IAS and the VA and IMA when the L-SCA is being treated), as well as flow hemodynamics and collateral patterns, are reviewed. Special attention is given to the lesion characteristics, such as length, involvement of the ostium, presence of thrombus, atheromatous material or heavy calcification, and proximal artery angulation, as well as the aortic arch type, orientation, and calcifications. Because peripheral vascular disease is common in these patients, access options are also evaluated. The innominate artery is short (2–5 cm) and larger in diameter than

TABLE 19.2 Endovascular and Open Surgical Treatment of Brachiocephalic Arteries³³

PROCEDURE	STUDIES (n)	PATIENTS (n)	MEAN FU (mo)	SURGICAL MORTALITY RATE (%)	CVA RATE (%)	10-YEAR SURVIVAL RATE (%)	PATENCY RATE (%)	TECHNICAL SUCCESS RATE (%)
Anatomic revascularization of the brachiocephalic arteries ²⁶	22	1650	58	7.8	3.8%	NA		
Carotid-subclavian transposition	8	381		0.4	1	83 (one study)	100 (one study)	
Carotid-subclavian bypass	18	1041	53.8	1.5	1.3	89 (four studies)	91 (five studies)	
Axillo-axillary bypass	16	426	51	0.5	1.1	90 (one study)	87 at 10 years (one study)	
Hybrid	9	173		7.9	6.9		100 at 1 year	
Endovascular	26	1305 (1379 lesions)	31					94 (stenosis) 64 (occlusion)

CVA, Cerebrovascular accident; FU, follow-up.

the L-SCA. It gives rise to the right carotid, subclavian, and vertebral subdivisions. It is also usually highly calcified and can be tortuous with a difficult takeoff depending on the aortic arch pattern. Therefore, it is more challenging to treat endovascularly compared with the L-SCA.

Since endovascular therapy for SCS usually involves stenting, patients are started on ASA 81 mg/day and clopidogrel 75 mg/day 5 days before the procedure. We carefully perform a complete preprocedure and postprocedure neurologic and ipsilateral upper extremity examination to assess for possible periprocedure complications. The procedure is performed generally under conscious sedation, and we apply the same sedation protocols employed in cardiac catheterization procedures.

The common femoral artery is the preferred primary route in most cases, when possible. Depending on patient's body habitus and degree of iliac artery and aortic tortuosity, a long (60 or 90 cm) 6-Fr sheath is placed for better catheter stability. After access is obtained, unfractionated heparin boluses are given to maintain an activated clotting time of 250–300 seconds. A complete aortic arch angiogram is then performed (using DSA technique, LAO projection at 30–45 degrees to avoid foreshortening of the aortic arch seen with AP projection. Inject 10 cc/sec for 20 cc at 1000 PSI) to define aortic arch anatomy, confirm the exact location, length, and severity of the stenotic lesion and collateral pathways, and decide on best catheter to use for engagement. Late-phase angiography allows for documentation of retrograde flow in the VA (or via branches of the carotid system).

Given the considerable movement of the ascending portion of the left SCA during respiration, which can occasionally cause kinking of the proximal segment during expiration, we perform angiography during breath hold immediately after expiration. The quality of the image depends on the patient's ability to comply.

Identifying fluoroscopic landmarks can facilitate engagement of the destination vessel. The left SCA extends from the aorta (along the left side of the mediastinum) to the outer edge of the first rib, and the right brachiocephalic trunk arises on a level with the upper border of the second

right costal cartilage and ascends obliquely upward over the trachea. It divides at the level of the upper border of the right sternoclavicular articulation.

We approach the lesion with a 6-Fr guiding catheter, and an exchange-length 0.035-inch hydrophilic wire is used to traverse the stenosis in antegrade fashion. The wire tip is positioned in the axillary artery or beyond, within the fluoroscopic field of view, to provide stability to the system. The hydrophilic wire can then be exchanged to a supportive nonhydrophilic 0.035-inch wire for safety. Balloon angioplasty is then carried out with a properly sized balloon (for the reconstituted SCA). When predilation is deemed satisfactory, we telescope the sheath across the lesion (slowly and carefully over the supportive 0.035 to avoid guide dissection), position the stent, pull back the sheath (unsheath the stent to avoid dislodging balloon expanding stent from its balloon, especially in a calcified lesion), and deploy the stent in the usual fashion. Tight calcific lesions and an unstable guiding catheter system may not allow passage of the intended balloon. Therefore, preliminary dilation with a smaller (2- or 4-mm) balloon may facilitate delivery of the larger balloon. We typically dilate the balloon slowly to complete expansion. When severely calcified lesions are seen on angiography or IVUS and they do not yield with balloon predilatation, use of intravascular lithotripsy balloon dilatation can be helpful in ensuring adequate predilatation and stent expansion.^{41–44}

Notably, when poststenotic dilatation is present, stent sizing should match the nondilated (proximal) segment of the SCA. Proper sizing can be further evaluated by studying the CTA images or, preferably, by performing intraprocedural IVUS. Care should be taken when relying on CTA vessel sizing to ensure that the measurements were taken perpendicular to the vessel and the patient's hemodynamic state during the CTA study are like those during the procedure.

A steep contralateral cranial view is used to identify the relationship to the LIMA and vertebral ostia (RAO 30–40 and CRA 10–20 for LSCA), and an ipsilateral caudal view (LAO 3–40 and CAU 15–20 for LSCA) is used to identify the subclavian artery ostia. To visualize the bifurcation of the



right innominate artery (and R-CCA and R-SCA ostia), and ipsilateral (RAO projection) is utilized. Using road mapping further facilitates accurate stent positioning. We then deploy a balloon-expandable stent (BES) to ostial and proximal lesions as they allow for precise placement and provide adequate radial force, particularly when the SCA ostium is involved. We routinely allow the proximal edge of the BES to protrude into the aortic arch by about 1 to 2 mm to ensure coverage of the plaque extension into the aortic arch wall (common in ostial lesions) and compensate for potential stent foreshortening with postdilatation.⁴⁵ We usually oversize the stent by 1 mm while the postdilatation balloon matches the vessel size. We usually tolerate a mild waist and avoid aggressive postdilatation, which can trigger the release of atheromatous debris.

Self-expanding stents (SESs) have excellent radial strength and flexibility compared with BES. Therefore, we use them in lesions distal to the VA because these sites are subject to movement that may incur significant stress on the stent, increasing the risk of stent fractures. The SCA distal to the VA origin often has hinge points that can predispose the stents to fractures, therefore, when treating such lesions we accept a reasonable balloon angioplasty and avoid stenting SES are also used for lesions involving the axillary and brachial arteries and for lesions longer than 40 mm. Covered stents are reserved to repair direct injuries to the SCA, axillary, or brachial arteries. Occasionally, covered stents are used for heavily calcific ostial and proximal lesions and for in-stent restenosis when adequate landing zone away from the VA origin exists. Covered stents however require a 7F delivery system.

We always avoid jailing the VA, to prevent VA closure by plaque shift or embolization. In cases of associated severe VA origin stenosis, however, we use the ipsilateral radial access and employ the “kissing balloon” technique with or without distal emboli protection (DEP) device. After the DEP device is deployed in the midcervical VA, we advance a coronary balloon over a 0.014-inch wire into the VA lesion and inflate both balloons simultaneously. The VA is accessed via the ipsilateral radial (or, rarely, brachial) artery, after placement of a 6-Fr sheath. If the VA PTA result is unsatisfactory, it can be stented with a coronary drug-eluting stent before the subclavian stent is deployed.^{46,47,48} There have been reports when a “blocking balloon” can be retrieved without complication after deploying the stent across the VA origin while the balloon remained inflated in the VA ostia. This was done in the unusual cases when the SCA lesion extended beyond the VA origin and the stent must be extended that far. A low-profile balloon (e.g., Specter XC balloon, Microvention Inc.) was used with success.

When engagement of the SCA ostium with the guiding catheter is unsuccessful, we use a longer 4-Fr diagnostic catheter (JR4, vertebral or Vitek catheter) through the femoral 6-Fr guide or shuttle sheath. We then try to engage the ostium of the SCA with the 4-Fr catheter to support wire passage. When wire crossing is unsuccessful despite several careful attempts, which is usually the case in complete (flush) occlusion, when severe ostial SCA stenosis (string sign; Figure 19.3) or when severe tortuosity is present, we combine the transfemoral antegrade with a transbrachial (or transradial) retrograde approach. In a large series of 170

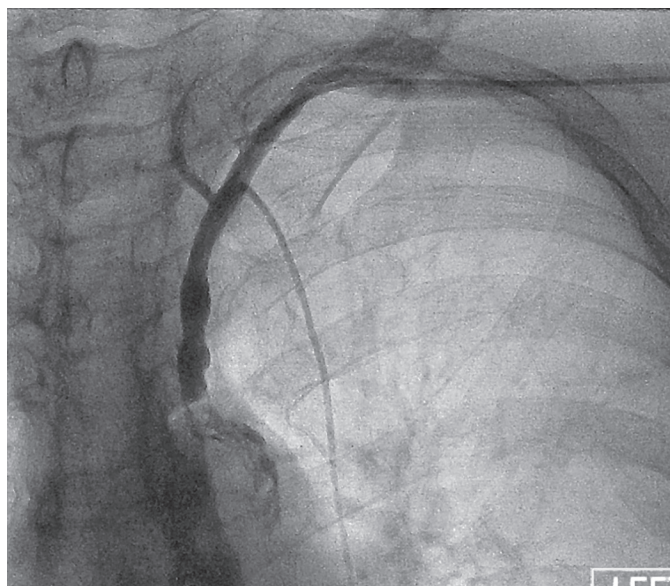


FIGURE 19.3 String sign indicative of very severe stenosis in the left subclavian artery.

patients treated between 1993 and 2006, revascularization was attempted on 177 subclavian or innominate arteries (98% and 6%, respectively). The retrograde approach, mainly via the radial (occasionally brachial) artery, was used in 13 of 21 (62%) total occlusion cases.⁴⁹

Given the diminished radial (and brachial) pulses imposed by the proximal subclavian artery occlusion, we always use ultrasonographic guidance when accessing the ipsilateral radial (or brachial) artery. An adequate length sheath is advanced over the wire and positioned proximal to the VA origin. Simultaneous angiography (via the transfemoral guiding catheter and the transbrachial sheath) is performed to delineate the length of the occlusion and its anatomic characteristics. Using these images, we carefully advance the transfemoral sheath and reattempt to cross the lesion antegrade. If this is unsuccessful, we then proceed to cross the lesion retrogradely. The radial (or brachial) sheath is advanced carefully to engage the distal cap of the occlusion and the stiff guidewire (usually 0.014 but 0.018 or 0.035 inch wires are occasionally used) is carefully advanced through the occlusion into the descending aorta. Based on lesion characteristics, this may be done while a blocking balloon is inflated in the origin of the VA (see earlier). We frequently evaluate the course of the wire during its passage by switching between anteroposterior to angulated views to ensure continued intraluminal position. This is important as the wire can rarely cause aortic dissection as it exits the L-SCA ostia (Figure 19.4). Once distal wire position is confirmed in the descending aortic lumen, the wire is snared and externalized through the transfemoral sheath. The wire is reversed, and the soft tip is placed alongside the radial (or brachial) sheath. We then complete the procedure via antegrade fashion since it allows for accurate stent positioning. Another reason to complete the procedure via antegrade access is to have the option to deploy a covered stent if needed (ex. perforation), which requires a larger access site that can be challenging to achieve radially. However, in cases when femoral access is

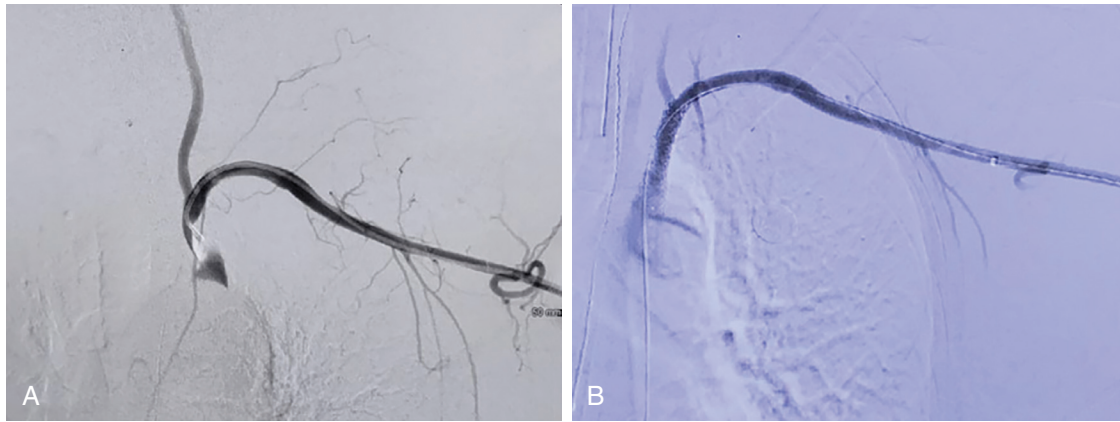


FIGURE 19.4 **A**, Contrast staining of the aortic wall noted after retrograde crossing from the brachial access. **B**, Successful stenting of left subclavian artery stenosis via upper extremity access with tacked appearance of the aortic wall after proximal stent flaring.



FIGURE 19.5 Left subclavian artery angioplasty and stenting completed from left upper extremity access. **A**, Retrograde angiography performed via retrograde catheter placed proximal to the vertebral artery. **B**, Stent positioned under roadmap guidance. **C**, Poststent angiography.

not an option because of severe iliac or aortic disease, the entire procedure can be completed radially (Figure 19.5).

When treating a primarily thrombotic lesion, we consider introducing an emboli protection device (EPD) through the right brachial (or radial) sheath and deploy it into the midcervical VA as long as the VA diameter is greater than 3.5 mm. When thrombus aspiration is considered, we typically do this via the radial or brachial access sheath.

In cases of innominate artery occlusion, both femoral arteries are commonly accessed so that a diagnostic catheter can be used for contrast injection while the interventional catheter engages the proximal cap of the occlusive plaque, and the interventional wire is advanced. If EPDs to the carotid or VAs are desired, this can be advanced via a 6-Fr catheter from the ipsilateral radial access, particularly when the occlusive plaque is near the right internal carotid artery origin.⁵⁰ After EPD is deployed, angioplasty and stenting are carried out as described. Upon achieving satisfactory results, the EPDs are retrieved in the usual fashion. We do not recommend using EPD in the VA through the

transfemoral approach because removal may be difficult because of the unusually high risk of device entrapment by the subclavian or innominate stent.⁵¹

Attention should be made to recognize and immediately treat potential EPD complications, such as vertebral or carotid artery spasm and dissection.⁵¹

The argument against using DEP in SCA and IA intervention relies largely on the early report of Ringelstein and Zeumer,⁵² which suggested that reversal of retrograde VA flow after SCA recanalization occurs gradually within 20 seconds to several minutes. A reasonable counterargument can be made that the protection provided by this brief delay is suboptimal and unreliable, particularly when thrombus is present, the lesion is mostly atheromatous, and intervention is performed on the right innominate artery when the right carotid artery is at risk.⁵² This counterargument is further supported by the observation that almost a quarter of the patients in Ringelstein and Zeumer's⁵² study (two of nine) had immediate restoration of antegrade vertebral flow as assessed by continuous ultrasound monitoring of the VA. Nonetheless, routine use of EPD is not mandatory



in all lesions, and the interventionalist should weigh the benefits of such approach against the potential risks and based on lesion characteristics, anatomy of the vessels, and the operator's personal skill and expertise.⁵¹

Generally, fibrotic lesions encountered in patients with FMD respond well to PTA alone. However, when angioplasty alone is used to treat subclavian and innominate artery lesions, adequate time⁴⁷ should be given to document persistent patency and absence of vessel recoil or closure before terminating the procedure.⁴⁷ In atherosclerotic lesions, in which calcifications are common, stenting reduces acute closure, improves patency rates, facilitates recanalization of restenotic lesions, and reduces the risk of distal embolization by trapping debris between stent struts and the arterial wall during stent expansion. Based on the latter benefit, some authors went as far as advocating direct stenting of moderately calcified SAS and IAS.²⁹ The author, however, prefers balloon angioplasty first, occasionally with an undersized balloon, to facilitate stent sizing and ensure reasonable vessel prep.

Technical success is usually defined as 30% or less residual stenosis and lowering the BBPD (to ≤ 10 mm Hg) and the pressure gradient (≤ 5 mm Hg). Clinical success is defined as improvement or resolution of the symptoms that justified the revascularization procedure.⁵³ In a single-center study that evaluated trends and outcomes of subclavian revascularization in 114 patients who underwent 137 procedures, Palchik et al.³⁸ reported that the endoluminal approach became the predominant method since 2004 and that most procedures in recent years were performed for either arm ischemia or cardiac indication.

The initial procedural success rates with endovascular therapy of subclavian and innominate artery stenosis is around 93% to 100%,^{49,54-60} averaging 94%,³³ and 83% to 94% for occlusions.^{4,33,39,40,49,61} A recent large series published by Patel et al.⁴⁹ showed an intermediate (3-year) patency rate of 83%. Other series confirmed long-term (5–10 years) patency rates between 80% to 90%, with better results achieved with stenting compared with angioplasty alone.^{38,48,56,57}

Overall complication rates of endovascular interventions are significantly lower compared with open surgical procedures and range between 0% and 10%.^{38,49,54,60,62-69} Potential complications include major and minor stroke (ischemic or hemorrhagic); transient ischemic attack; access site hematoma; pseudoaneurysm or AV fistula; radial, brachial, or axillary artery thrombosis; dissection or perforation of the SCA or the aorta; and digital ischemia caused by distal embolic events and arm edema secondary to reperfusion injury. Dissection or perforation of the aortic arch is very rare and more likely to be seen with interventions performed on an occluded subclavian artery (Figure 19.4).

Rarely, stent fractures and distal embolization have been reported.⁷⁰ These events are likely related to compression forces exerted by the clavicle and first rib on the stented lateral segment of the subclavian vessels as it traverses between these structures. The phenomenon was described in stented subclavian arteries and veins and reported with all types of stents, including BESs, SESs, and covered stents.^{70,71} Nonetheless, the author agrees that the SES memory makes it more likely to resume its configuration after deformation and continue to recommend using

SES for the distal segment of the SCA if stenting is warranted.⁷⁰

When stent restenosis or occlusion develops in patients with extensive disease, carotid–subclavian bypass surgery with a prosthetic graft is commonly performed and yields favorable outcomes, (5-year patency rate, 97%).^{72,73}

After intervention, we maintain patients on dual antiplatelet therapy (DAPT) for a minimum of 1 month. However, most such patients have diffuse and residual atherosclerotic disease in other vascular beds, and these often carry with them indications for longer DAPT or other combinations of antiplatelet and antithrombotic therapy. Baby aspirin and clopidogrel are the most commonly prescribed combination post SCA stenting.

Considering the absence of randomized controlled trials comparing endovascular versus open surgical treatment of symptomatic atherosclerotic SAS, Galyfos et al.⁷⁴ performed a systemic review of seven medium- and high-quality clinical studies published before 2018. They compared early and late major outcomes in 731 patients (463 underwent open and 297 endovascular procedures). With regard to early procedural outcomes, the authors reported an excess of peripheral nervous system events, specifically laryngeal, phrenic, or cranial nerve palsy or injury and Horner syndrome in the surgical group (5.4% vs 0.2%), but primary patency, death, cardiac events, central nervous system events, and access site complications were similar between the two groups. As for mid- and long-term outcomes the surgical group had better primary patency at 1, 3, and 5 years, but no significant differences were noted in 5-year survival rates and recurrent symptoms at 5 years. The findings of this review provided assurance that endovascular therapy is a feasible and safe strategy for treating many patients with this condition.

CONCLUSIONS

In summary, atherosclerosis is the most common cause of upper extremity occlusive disease, and revascularization procedures are an integral part of contemporary practice. Symptomatic individuals presenting with upper extremity ischemia, neurologic symptoms, threatened hemodialysis or axillary-femoral bypass grafts, or coronary insufficiency caused by compromised flow to a LIMA graft should be considered for treatment. Endovascular therapy is the treatment of choice in most but not all cases, and excellent results can be achieved with careful patient selection, thoughtful procedure planning, and when experienced operators follow best practices, including the retrograde upper extremity approach and the use of EPD when appropriate.

REFERENCES

1. Osborn LA, Vernon SM, Reynolds B, et al. Screening for subclavian stenosis in patients who are candidates for coronary bypass surgery. *Cathet Cardiovasc Intervent*. 2002;56:162-165.
2. Shadman R, Criqui MH, Bundens WP, et al. Subclavian stenosis: the prevalence, risk factors and association with other cardiovascular diseases. *J Am Coll Cardiol*. 2004;44:618-623.
3. Schillinger M, Haumer M, Schillinger S, et al. Outcome of conservative versus interventional treatment of subclavian artery stenosis. *J Endovasc Ther*. 2002;9:139-146.

4. Ochoa VM, Yeghiazarians Y. Subclavian artery stenosis: a review for the vascular medicine practitioner. *Vasc Med*. 2011;16:29-34.
5. Labropoulos N, Nandivada P, Bekelis K. Prevalence and Impact of the subclavian steal syndrome. *Ann Surg*. 2010;252:166-170.
6. Wylie EJ, Effeney DJ. Surgery of the aortic arch branches and vertebral arteries. *Surg Clin North Am*. 1979;59:669-680.
7. Hass WK, Fields WS, North RR, et al. Joint study of extracranial arterial occlusion. II. Arteriography, techniques, sites, and complications. *JAMA*. 1968;203:961-968.
8. Aboyans V, Criqui MH, McDermott MM, et al. The vital prognosis of subclavian stenosis. *J Am Coll Cardiol*. 2007;49:1540-1545.
9. Gutierrez GR, Mahrer P, Aharonian V, et al. Prevalence of subclavian artery stenosis in patients with peripheral vascular disease. *Angiology*. 2001;52(3):189-194.
10. Clark CE, Taylor RS, Shore AC, et al. Association of a difference in systolic blood pressure between arms with vascular disease and mortality: a systematic review and meta-analysis. *Lancet*. 2012;379:905-914.
11. English JA, Carell ES, Guidera SA, et al. Angiographic prevalence and clinical predictors of left subclavian stenosis in patients undergoing diagnostic cardiac catheterization. *Catheter Cardiovasc Interv*. 2001;54:8-11.
12. Sharma BK, Jain S, Suri S, et al. Diagnostic criteria for Takayasu arteritis. *Int J Cardiol*. 1996;54(suppl):S141-S147.
13. Nuenninghoff DM, Hunder GG, Christianson TJ, et al. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. *Arthritis Rheum*. 2003;48:3522-3531.
14. Backer CL, Mavroudis C. Coarctation of the aorta and interrupted aortic arch. In: Baue AE, Geha AS, Hammond GI, et al., eds. *Glenn's Thoracic and Cardiovascular Surgery*. Stamford, Connecticut: Appleton and Lange; 1996:1244-1247.
15. Durham JR, Yao JST, Pearce WH, et al. Arterial injuries in the thoracic outlet syndrome. *J Vasc Surg*. 1995;21:57-70.
16. Rubin DI, Scomberg PJ, Shepherd RF, et al. Arteritis and brachial plexus neuropathy as delayed complications of radiation therapy. *Mayo Clin Proc*. 2001;76:849-852.
17. Rice RD, Armstrong PJ. Brachial artery fibromuscular dysplasia. *Ann Vasc Surg*. 2010;24:255.e1-e4.
18. Nakagawa M, Osawa Y, Hanato T, et al. Association of aortic arch anomalies and subclavian artery supply disruption with neurofibromatosis. *Int J Cardiol*. 2005;104:32-34.
19. Lord RSA, Adar R, Stein RL. Contribution of the circle of Willis to the subclavian steal syndrome. *Circulation*. 1969;40:871-878.
20. Goldenberg E, Arlazoroff AR, Pajewski M, et al. Unusual clinical signs in left subclavian artery occlusion: clinical and angiographic correlation. *Stroke*. 1983;14(3):396-398.
21. Cherry KJ Jr, McCullough JL, Hallett JW Jr, et al. Technical principles of direct innominate artery revascularization: a comparison of endarterectomy and bypass grafts. *J Vasc Surg*. 1989;9(5):718-723.
22. Javid H, Julian OC, Dye WS, et al. Management of cerebral arterial insufficiency caused by reversal of flow. *Arch Surg*. 1965;90:634-643.
23. Guilbert MC, Elkouri S, Bracco D, et al. Arterial trauma during central venous catheter insertion: case series, review and proposed algorithm. *J Vasc Surg*. 2008;48:918-925.
24. Cayne NS, Berland TL, Rockman CB, et al. Experience and technique for the endovascular management of iatrogenic subclavian injury. *Ann Vasc Surg*. 2010;24:44-47.
25. Park H, Kim HJ, Chan MJ, et al. A case of cerebellar infarction caused by acute subclavian thrombus following minor trauma. *Yonsei Med J*. 2013;54(6):1538-1541.
26. Klocker J, Falkensammer J, Pellegrini L, et al. Repair of arterial injury after blunt trauma in the upper extremity—immediate and long-term outcome. *Eur J Vasc Endovasc Surg*. 2010;39:160-164.
27. Cooper DG, Walsh SR, Sadat U, et al. Neurological complications after left subclavian artery coverage during thoracic endovascular aortic repair: a systematic review and meta-analysis. *J Vasc Surg*. 2009;49:1594-1601.
28. Schillinger M, Haumer M, Schillinger S, et al. Outcome of conservative versus interventional treatment of subclavian artery stenosis. *J Endovasc Ther*. 2002;9:139-146.
29. Sixt S, Rastan A, Schwarzwälder U, et al. Long term outcome after balloon angioplasty and stenting of subclavian artery obstruction: a single center experience. *Vasa*. 2008;37:174-182.
30. De Bakey ME, Crawford ES, Fields WS. Surgical treatment of patients with cerebral arterial insufficiency associated with extracranial arterial occlusive lesions. *Neurology*. 1961;11:145-149.
31. Crawford ES, DeBakey ME, Morris GC, et al. Surgical treatment of occlusion of the innominate, common carotid, and subclavian arteries: a 10-year experience. *Surgery*. 1969;65:17-31.
32. Berguer R, Morasch MD, Kline RA, et al. Cervical reconstruction of the supra aortic trunks: a 16-year experience. *J Vasc Surg*. 1999;29:239-248.
33. Aziz F, Gravett MH, Comerota AJ. Endovascular and open surgical treatment of brachiocephalic arteries. *Ann Vasc Surg*. 2011;25:569-581.
34. Cooper DG, Walsh SR, Sadat U, et al. Neurological complications after left subclavian artery coverage during thoracic endovascular aortic repair: a systematic review and meta-analysis. *J Vasc Surg*. 2009;49:1594-1601.
35. De Bakey ME, Crawford ES, Cooley DA, et al. Surgical considerations of occlusive disease of innominate, carotid, subclavian, and vertebral arteries. *Ann Surg*. 1959;149:690-710.
36. Chang JB, Stein TA, Liu JP, et al. Long-term results with axillo-axillary bypass grafts for symptomatic subclavian artery insufficiency. *J Vasc Surg*. 1997;25:173-178.
37. Cina CS, Hussein SA, Lagana A, et al. Subclavian carotid transposition and bypass grafting: consecutive cohort study and systematic review. *J Vasc Surg*. 2002;35:422-429.
38. Palchik E, Bakken AM, Wolford HY, et al. Subclavian artery revascularization: an outcome analysis based on mode of therapy and presenting symptoms. *Ann Vasc Surg*. 2008;22:70-78.
39. Bachman DM, Kim RM. Transluminal dilatation for subclavian steal syndrome. *AJR Am J Roentgenol*. 1980;135:995-996.
40. Mathias KD, Luth I, Haarmann P. Percutaneous transluminal angioplasty of proximal subclavian artery occlusions. *Cardiovasc Intervent Radiol*. 1993;16:214-218.
41. Khan MS, Baig M, Moustafa A, et al. Intravascular Lithotripsy in Calcified Subclavian and Innominate Peripheral Artery Disease: A Single-Centre Experience. *Cardiovasc Revasc Med*. 2022;40:37-41. doi:10.1016/j.carrev.2021.11.029.
42. Bellini B, Tzanis G, Ancona MB, Carlino M, Azzalini L, Montorfano M. Calcific Lesions of the Subclavian Artery: The Potential Role of Intravascular Lithotripsy. *JACC Cardiovasc Interv*. 2019;12(15):1513-1515. doi:10.1016/j.jcin.2019.03.019.
43. Case BC, Yerasi C, Forrestal BJ, et al. Intravascular Lithotripsy Facilitated Percutaneous Endovascular Intervention of the Aortic Arch: A Single-Center Experience. *Cardiovasc Revasc Med*. 2020;21(8):1006-1015. doi:10.1016/j.carrev.2020.04.029.
44. Varotto L, De Boni A, Iannucci G, Caprioglio F. Uncommon intravascular lithotripsy for the treatment of subclavian steal syndrome: a case presenting with concomitant acute coronary syndrome and transient ischaemic attack. *Eur Heart J*. 2022;43(8):840. doi:10.1093/eurheartj/ehaa1082.
45. Brountzos EN, Malagari K, Kelekis DA. Endovascular treatment of occlusive lesions of the subclavian and innominate arteries. *Cardiovasc Intervent Radiol*. 2006;29(4):503-510.
46. Henry M, Henry I, Klonaris C, et al. Percutaneous transluminal angioplasty and stenting of extracranial VA stenosis. In: Henry M, Ohki T, Polydorou A, eds. *Angioplasty and Stenting of the Carotid and Supra-aortic Trunks*. 1st ed. London: Taylor and Francis Medicine; 2004:673-682.
47. Dabus G, Moran CJ, Derdeyn CP, et al. Endovascular treatment of vertebral artery-origin and innominate/subclavian disease: indications and technique. *Neuroimaging Clin N Am*. 2007;17:381-392, ix.
48. Staikov IN, Do DD, Remonda L, et al. The site of atheromatosis in the subclavian and vertebral arteries and its implication for angioplasty. *Neuroradiology*. 1999;41(7):537-542.
49. Patel SN, White CJ, Collins TJ, et al. Catheter-based treatment of the subclavian and innominate arteries. *Catheter Cardiovasc Interv*. 2008;71:963-968.
50. Albuquerque FC, Ahmed A, Stiefel M, et al. Endovascular recanalization of the chronically occluded brachiocephalic and subclavian arteries: technical considerations and an argument for embolic protection. *World Neurosurg*. 2013;6:e327-e336.
51. Dumontl TM, Eller JL, Hopkins LN. Embolic protection for great vessel revascularization: is this best practice? *World Neurosurg*. 2013;80(6):e199-e200.
52. Ringelstein EB, Zeumer H. Delayed reversal of vertebral artery blood flow following percutaneous transluminal angioplasty for subclavian steal syndrome. *Neuroradiology*. 1984;26:189-198.
53. Aiello F, Morrissey NJ. Open and endovascular management of subclavian and innominate arterial pathology. *Semin Vasc Surg*. 2011;24:31-35.
54. Rodriguez-Lopez JA, Werner A, Martinez R, et al. Stenting for atherosclerotic occlusive disease of the subclavian artery. *Ann Vasc Surg*. 1999;13:254-260.
55. Westerband A, Rodriguez JA, Ramaiah VG, et al. Endovascular therapy in prevention and management of coronary-subclavian steal. *J Vasc Surg*. 2003;38:699-704.
56. Berger L, Bouziane Z, Felisaz A, et al. Long-term results of 81 prevertebral subclavian artery angioplasties: a 26-year experience. *Ann Vasc Surg*. 2011;25:1043-1049.
57. deVries JP, Jager LC, van den Berg JC, et al. Durability of percutaneous transluminal angioplasty for obstructive lesions of proximal subclavian artery: long-term results. *J Vasc Surg*. 2005;41:19-23.
58. Miyakoshi A, Hatano T, Tsukahara T, et al. Percutaneous transluminal angioplasty for atherosclerotic stenosis of the subclavian or innominate artery: angiographic and clinical outcomes in 36 patients. *Neurosurg Rev*. 2012;35:121-126.
59. Huttli K, Nemes B, Simonffy A, et al. Angioplasty of the innominate artery in 89 patients: experience over 19 years. *Cardiovasc Intervent Radiol*. 2002;25(2):109-114.
60. Brountzos EN, Petersen B, Binkert C, et al. Primary stenting of subclavian and innominate artery occlusive disease: a single center's experience. *Cardiovasc Intervent Radiol*. 2004;27(6):616-623.
61. Martinez R, Rodriguez-Lopez J, Torruella L, et al. Stenting for occlusion of the subclavian arteries. *Tex Heart Inst J*. 1997;24:23-27.
62. Amor M, Eid-Lidt G, Chati Z, et al. Endovascular treatment of the subclavian artery: stent implantation with or without predilatation. *Catheter Cardiovasc Interv*. 2004;63(3):364-370.
63. Brountzos EN, Malagari K, Kelekis DA. Endovascular treatment of occlusive lesions of the subclavian and innominate arteries. *Cardiovasc Intervent Radiol*. 2006;29(4):503-510.



64. Bates MC, Broce M, Lavigne PS, et al. Subclavian artery stenting: factors influencing long-term outcome. *Catheter Cardiovasc Interv.* 2004;61(1):5-11.
65. Przewlocki T, Kablak-Ziembicka A, Pieniazek P, et al. Determinants of immediate and long-term results of subclavian and innominate artery angioplasty. *Catheter Cardiovasc Interv.* 2006;67:519-526.
66. Sixt S, Rastan A, Schwarzwald U, et al. Results after balloon angioplasty or stenting of atherosclerotic subclavian artery obstruction. *Cathet Cardiovasc Interv.* 2009;73:395-403.
67. AbuRahma AF, Bates MC, Stone PA, et al. Angioplasty and stenting versus carotid-subclavian bypass for the treatment of isolated subclavian artery disease. *J Endovasc Ther.* 2007;14:698-704.
68. Henry M, Amor M, Henry I, et al. Percutaneous transluminal angioplasty of the subclavian arteries. *J Endovasc Surg.* 1991;6:33-41.
69. Gonzalez A, Gil-Peralta A, Gonzalez-Marcos JR, et al. Angioplasty and stenting for total symptomatic atherosclerotic occlusion of the subclavian or innominate arteries. *Cerebrovasc Dis.* 2002;13:107-113.
70. Phipp LH, Scott DJ, Kessel D, et al. Subclavian stents and stent-grafts: cause for concern? *J Endovasc Surg.* 1999;6:223-226.
71. Hinke DH, Zandt-Stastny D, Goodman LR. Pinch-off syndrome: a complication of implantable subclavian venous access devices. *Radiology.* 1990;177:353-356.
72. Modarai B, Ali T, Dourado R, Reidy JF, Taylor PR, Burnand KG. Comparison of extra-anatomic bypass grafting with angioplasty for atherosclerotic disease of the supra-aortic trunks. *Br J Surg.* 2004;91:1453-1457.
73. Aboyans V, Ricco J, Bartelink M, et al. ESC Scientific Document Group, 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J.* 2018;39(9):763-816.
74. Galyfos GC, Kakisis I, Maltezos C, Geroulakos G. Open versus endovascular treatment of subclavian artery atherosclerotic disease. *J Vasc Surg.* 2019; 69:269-279.



20

Renal Artery Intervention: Catheter-Based Therapy For Renal Artery Stenosis

CHRISTOPHER J. WHITE

INTRODUCTION, 371

DIAGNOSIS, 371

Screening for Renal Artery Stenosis, 371

Duplex Ultrasonography, 371

Resistive Index, 372

Noninvasive Angiography, 372

Invasive Angiography, 373

Translesional Pressure Gradients, 373

RENAL ARTERY INTERVENTION, 373

Technique for Renal Artery Intervention, 374

Renal Artery Atherosclerotic Lesions, 374

Fibromuscular Dysplasia, 375

Procedural Complications, 375

Embolic Protection Devices, 375

Radial Artery Access, 375

Renal Artery In-Stent Restenosis, 376

ASYMPTOMATIC RENAL ARTERY STENOSIS, 376

RENOVASCULAR HYPERTENSION, 376

Clinical Characteristics, 376

Prevalence, 377

Epidemiology, 377

EVIDENCE-BASED TREATMENT, 377

ISCHEMIC NEPHROPATHY, 378

Prevalence, 378

Evidence-Based Treatment, 378

CARDIAC DESTABILIZATION SYNDROMES, 378

SUMMARY, 379

INTRODUCTION

A key principle governing renal artery stenting (RAS) is that clinical benefit will result from relieving a significant renal artery stenosis causing renal hypoperfusion. Published meta-analyses suggest that a very high RAS technical success rate (>95%) is accompanied by a surprisingly modest and inconsistent clinical improvement (Figure 20.1).¹ The discordance between the high technical success rate for RAS and the inconsistent clinical response suggests the following:

1. Successful RAS procedures were performed on nonobstructive RAS (stenoses not causing symptomatic renal hypoperfusion).
2. That the clinical syndrome being treated (hypertension or renal insufficiency) was not caused by renal hypoperfusion resulting in ischemia.

We must improve our ability to discriminate between ischemia-producing and nonsignificant renal artery stenoses if we hope to obtain concordance between the very high technical success rate of renal stenting and a clinical response.

DIAGNOSIS

Screening for Renal Artery Stenosis

Screening for renal artery stenosis is appropriate in patients at increased risk for this disease (Table 20.1).² Whenever possible, screening tests for renal artery stenosis should be performed noninvasively using direct imaging tests such as Doppler ultrasonography (DUS), computed tomography angiography (CTA), or magnetic resonance angiography (MRA). Noninvasive imaging has become so sophisticated and accurate that it is seldom necessary to

perform catheter-based angiography for the diagnosis of renal artery stenosis.

The appropriateness of screening angiography for RAS at the time of cardiac or peripheral vascular angiography of other vascular beds has been addressed by recommendations and guidelines endorsed by an expert consensus panel of several specialty societies.^{2,4} For patients with risk factors as outlined in Table 20.1² or clinical syndromes suggestive of RAS, aortography is given a Class I indication for screening at the time of angiography performed for other clinical indications, but ideally in these patients with planned elective procedures, DUS will be performed before the invasive procedure.²

Duplex Ultrasonography

Duplex ultrasonography is an excellent test to detect renal artery stenosis but is highly dependent on the skill of the technician performing the test and the time allotted to the technician to perform a thorough examination. It is the least expensive of the imaging modalities and provides useful information about the degree of stenosis, the pole-to-pole kidney size, and other associated disease processes. The location and severity of stenosis can accurately be determined by DUS of the renal artery.

Overall, compared with angiography, DUS has a sensitivity and specificity of 84% to 98% and 62% to 99%, respectively, when used to diagnose renal artery stenosis. Renal artery DUS is an excellent test for the follow-up of RAS after revascularization. After renal stenting, a renal artery DUS should be obtained within the first few weeks to establish a new baseline, at 6 months, 12 months, and yearly thereafter.⁵

One drawback of DUS is that the sensitivity is lower for identifying accessory renal arteries (67%) compared with

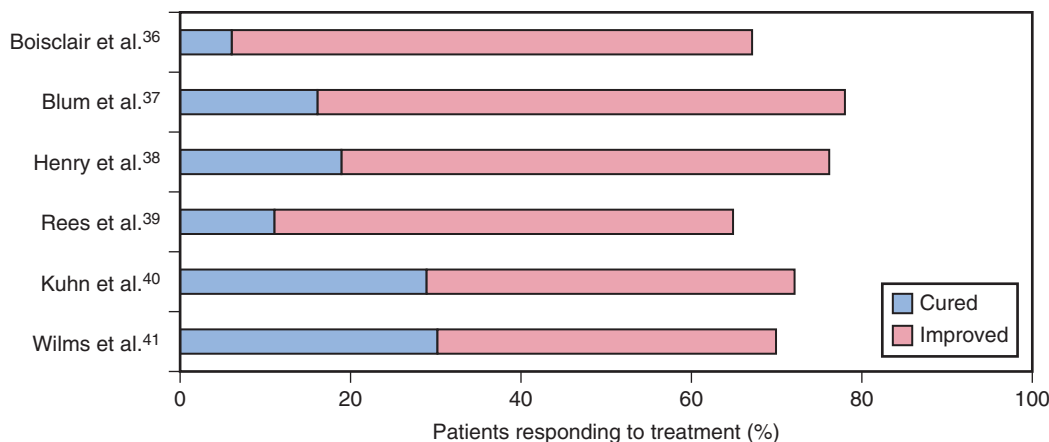


FIGURE 20.1 Hypertension response to renal intervention. Graphic representation of the cure and improvement rate after renal artery stenting (RAS).³⁶⁻⁴¹ (From Boisclair C, Therasse E, Oliva VL, et al. Treatment of renal angioplasty failure by percutaneous renal artery stenting with Palmaz stents: midterm technical and clinical results. *AJR Am J Roentgenol.* 1997;168:245-251; Blum U, Krumme B, Flugel P, et al. Treatment of ostial renal-artery stenoses with vascular endoprotheses after unsuccessful balloon angioplasty [see comments]. *N Engl J Med.* 1997;336:459-465; Henry M, Amor M, Henry I, et al. Stent placement in the renal artery: three-year experience with the Palmaz stent. *J Vasc Interv Radiol.* 1996;7:343-350; Rees CR, Palmaz JC, Becker GJ, et al. Palmaz stent in atherosclerotic stenoses involving the ostia of the renal arteries: preliminary report of a multicenter study. *Radiology.* 1991;181:507-514; Kuhn FP, Kutkuhn B, Torsello G, et al. Renal artery stenosis: preliminary results of treatment with the Strecker stent. *Radiology.* 1991;180:367-372; and Wilms GE, Peene PT, Baert AL, et al. Renal artery stent placement with use of the Wallstent endoprosthesis. *Radiology.* 1991;179:457-462.)

TABLE 20.1 Increased Prevalence of Renal Artery Stenosis

- Onset of hypertension at 30 years or younger or 55 years or older
- Malignant, accelerated, or resistant hypertension
- Unexplained renal dysfunction
- Development of azotemia with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker medication
- Unexplained pole to pole diameter discrepancy of ≥ 1.5 cm between kidneys
- Cardiac disturbance syndrome (flash pulmonary edema)
- Peripheral arterial disease (abdominal aortic aneurysm or ankle brachial index <0.9)
- Multivessel (two or more) coronary artery disease

main renal arteries (98%). Therefore, if the patient has hypertension that cannot be adequately controlled with a guideline-directed medical therapy (GDMT) and the DUS fails to demonstrate RAS, another imaging modality (CTA or MRA) may be considered to rule out stenosis of an accessory renal artery.

Detecting renal artery in-stent restenosis is a potential problem when native vessel DUS velocity parameters are used for diagnosis. A cohort of 132 patients with renal artery stents had angiographic correlation with DUS findings.⁶ There was no single peak systolic velocity (PSV) cutoff that would accurately discriminate 60% to 99% from 0% to 59% restenosis in all patients. A PSV below 241 cm/s was useful in excluding in-stent restenosis (negative predictive value, 96%). A PSV of 296 cm/s or greater was accurate in predicting in-stent restenosis (positive predictive value, 94%). A PSV between 241 and 295 cm/s represented an indeterminate zone in which renal artery restenosis could not be diagnosed or excluded on the basis of DUS alone.

Resistive Index

The resistive index (RI) is obtained by measuring the PSV and the end-diastolic velocity within the renal parenchyma at the level of the cortical blood vessels. It is an indication of the amount of small vessel arterial disease (i.e., nephrosclerosis) within the renal parenchyma. A prospective study

of renal stent placement demonstrated that an elevated RI predicted a favorable blood pressure response and renal functional improvement at 1 year after renal arterial intervention.⁷ If there are good clinical reasons to revascularize a kidney, then it should be performed independently of the RI.

Noninvasive Angiography

Computed tomography angiography uses ionizing radiation and iodinated contrast to produce excellent cross-sectional images of the abdominal vasculature (Figure 20.2). CTA has a sensitivity and specificity for detecting RAS of 89% to 100% and specificity of 82% to 100%.⁴ Excellent three-dimensional image quality with enhanced resolution can be obtained with multidetector-row CTA technology.⁴ The advantages of CTA over MRA include higher spatial resolution, absence of flow-related phenomena that may overestimate the degree of stenosis, and the capability to visualize calcification and metallic implants such as endovascular stents and stent grafts. CTA is generally well tolerated with an open gantry, so claustrophobia is not as limiting a factor as it is for MRA. The disadvantages of CTA compared with MRA are exposure to ionizing radiation and the need to administer potentially nephrotoxic iodinated contrast agents.

Magnetic resonance angiography also provides excellent cross-sectional imaging of the abdominal vasculature and associated anatomical structures. Compared with angiography, MRA has demonstrated a sensitivity of 91% to 100% and a specificity of 71% to 100%.⁴ Contrast-enhanced MRA using gadolinium improves image quality when compared with noncontrast studies and shortens imaging time, thereby eliminating some of the artifact created by patient motion. However, MRA does not have the same sensitivity and specificity in patients with fibromuscular dysplasia (FMD) and is generally not a good screening test if FMD is suspected.

Gadolinium should not be used in patients with a glomerular filtration rate (GFR) less than 30 mL/min/1.73 m² because of the risk of developing nephrogenic systemic



FIGURE 20.2 Computed tomography angiography of the abdominal aorta showing bilateral renal arteries ($n = 5$). Note the stenosis of the right renal accessory artery (white arrow), that could be missed by duplex ultrasonography.

sclerosis.⁴ MRA may not be used in patients with metallic (ferromagnetic) implants such as some mechanical heart valves, cerebral aneurysm clips, and electrically activated implants (pacemakers, spinal cord stimulators). MRA is not useful in following patients after stent implantation because of artifact produced by the metal stent.

Invasive Angiography

The “Achilles heel” of renal stenting is the inaccuracy of the visual estimation of the angiographic severity of renal stenoses. Even with quantitative measurement, angiography may be unable to discriminate between nonobstructive stenoses and clinically significant ones (Figure 20.3).⁸ Most would agree that interventionalists are able to identify

“critical” stenoses in renal arteries, but for moderately severe lesions (50%–70%), physiological confirmation with translesional hemodynamic measurements is necessary.⁹

Translesional Pressure Gradients

The pathophysiology of renovascular hypertension has been well understood since the experiments of Goldblatt and others. Modern confirmation of this cause and effect relationship was demonstrated by DeBruyne and colleagues, who performed an *in vivo* experiment that showed a threshold gradient (distal/aortic mean pressure ratio [P_d/P_a] ≤ 0.9) for the release of renin after graded renal artery obstruction.¹⁰ Other investigators have now established that hemodynamic parameters of significant renal artery stenosis (peak systolic gradient >21 mm Hg, renal fractional flow reserve of ≤ 0.8 , and a dopamine-induced hyperemic mean translesional gradient ≥ 20 mm Hg) are associated with clinical improvement after renal stenting in patients with moderate (50%–70%) renal artery stenoses.⁹

RENAL ARTERY INTERVENTION

Much confusion was brought to the field by the early introduction of percutaneous balloon angioplasty as a very successful treatment for renal artery FMD, but it suffered a moderately high failure rate for atherosclerotic renal artery stenosis. The overestimation of the success rate for atherosclerotic lesions led to underpowered clinical trials, making it very difficult to demonstrate successful treatment outcomes. Balloon angioplasty has been shown to be inferior to renal stenting in atherosclerotic renal artery stenosis because of significant lesion recoil of these ostial stenoses after balloon dilation.

Renal artery restenosis after stent placement is related to both acute gain and late loss, similar to coronary artery restenosis. Quantitative angiography on a series of 100 consecutive patients found that patients with patent renal arteries at follow-up had significantly larger renal stent minimal lumen diameters (MLDs) (4.9 ± 0.9 mm vs 4.3 ± 0.7 mm; $P = .025$) and had significantly less late loss (1.3 ± 0.9 mm vs 3.0 ± 1.4 mm; $P < 0.001$).¹¹ In the largest single

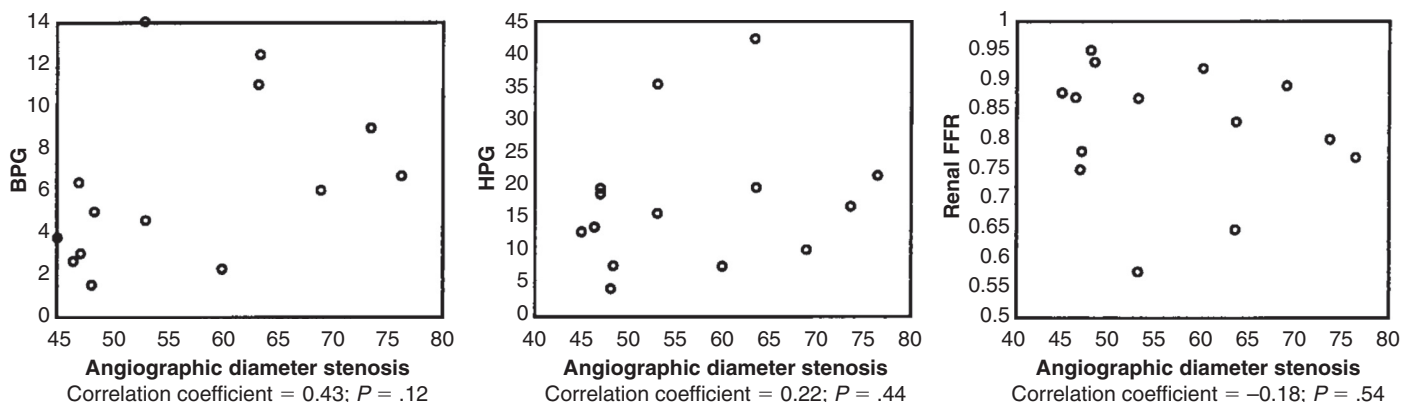


FIGURE 20.3 Lack of correlation between visual estimated renal artery stenosis and an objective measure of the hemodynamic gradient across the stenosis. FFR, fractional flow reserve. (Reproduced with permission from Subramanian R, White CJ, Rosenfield K, et al. Renal fractional flow reserve: a hemodynamic evaluation of moderate renal artery stenoses. *Catheter Cardiovasc Interv*. 2005;64:480-486.)

TABLE 20.2 Renal Stent Patency at 12 Months

REFERENCE	ARTERIES TREATED (n)	RESTENOSIS RATE (%)
Blum et al. ³⁷	74	11.0
Tuttle et al. ⁴²	148	14.0
Henry et al. ³⁸	209	11.4
Van de Ven et al. ⁴³	43	14.0
Rocha-Singh et al. ²⁰	180	12.0

From Blum U, Krumme B, Flugel P, et al. Treatment of ostial renal-artery stenoses with vascular endoprotheses after unsuccessful balloon angioplasty. *N Engl J Med*. 1997;336:459-465; Tuttle KR, Chouinard RF, Webber JT, et al. Treatment of atherosclerotic ostial renal artery stenosis with the intravascular stent. *Am J Kidney Dis*. 1998;32:611-622; Henry M, Amor M, Henry I, et al. Stent placement in the renal artery: three-year experience with the Palmaz stent. *J Vasc Interv Radiol*. 1996;7:343-350; Van de Ven PJ, Kaatee R, Beutler JJ, et al. Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. *Lancet*. 1999;353:282-286; and Rocha-Singh KJ, Mishkel GJ, Katholi RE, et al. Clinical predictors of improved long-term blood pressure control after successful stenting of hypertensive patients with obstructive renal artery atherosclerosis. *Catheter Cardiovasc Interv*. 1999;47:167-172.

series of renal stent implantation, a larger reference vessel diameter (RVD) and larger acute gain (i.e., post-stent MLD) after stent deployment were strongly associated with a lower incidence of restenosis. For example, restenosis in a vessel with an RVD less than 4.5 mm was 36% compared with only 6.5% for an artery with an RVD greater than 6.0 mm in diameter.¹² Renal stenting has been shown to be a durable treatment with 1-year patency rates of 85% or more (Table 20.2) and 5-year primary patency approaching 80%.¹

Percutaneous catheter-based therapy with primary stent placement has replaced open surgery as the treatment of choice for patients with atherosclerotic renal artery stenosis (Videos 20.1 and 20.2). However, despite a technical success rate exceeding 95% for renal artery stent placement, there remains wide variation in the reported success rates in improving hypertension. Although at least some of the variability in outcomes is attributable to a lack of standard reporting criteria, the dominant factors appear to be poor patient and lesion selection for treatment.¹ Variability in the angiographic assessment of the hemodynamic severity of renal artery stenoses has undermined the predictability of a treatment response with stenting. Although the majority of patients with hypertension and atherosclerotic renal artery stenosis and hypertension will experience improved blood pressure control or the need for fewer medications, very few patients will be cured of hypertension (see Figure 20.1).

Technique for Renal Artery Intervention

Aspirin is started at least 1 day before the procedure, and the use of dual antiplatelet therapy is at the discretion of the operator but is not supported by any evidence. Retrograde femoral access is most commonly chosen, although radial artery access is rapidly gaining acceptance (see further on). For retrograde common femoral artery access, a 6- or 7-Fr sheath is placed, and 3000 to 5000 U of unfractionated heparin is given to achieve a target activated clotting time of approximately 250 seconds. A 4-Fr diagnostic catheter (internal mammary or Judkins right coronary shape) is placed through a 6-Fr “short” (50- to 60-cm) angled (hockey-stick or renal-shaped) guiding catheter to

engage the ostium of the renal artery. A 0.014-inch coronary angioplasty guidewire is advanced across the lesion, and the guide catheter is then telescoped (advanced) over the 4-Fr diagnostic catheter, allowing the larger catheter to atraumatically engage the renal artery ostium.

A second technique for safely engaging the atherosclerotic renal ostium is the “no touch” technique. A 0.035-inch J-guidewire is advanced into the descending thoracic aorta above the renal arteries. The renal guide catheter is advanced over the J-wire until it is near the renal ostium. By gently manipulating (advancing and/or withdrawing) the 0.035-inch J-wire in the aorta, the tip of the guide catheter can be steered nearer to the renal artery ostium. When the guide is near the renal artery ostium, a 0.014-inch steerable guidewire is advanced through the guide catheter (alongside the 0.035-inch wire) and exiting the guide catheter near the ostium to enter into the renal artery and cross the stenosis into the distal portion of the renal artery. As the 0.035-inch guidewire is withdrawn, the guide catheter will atraumatically engage the renal ostium over the 0.014-inch wire.

Intravascular ultrasonography (IVUS) is a very useful tool for determining optimal stent sizing. A balloon sized 1:1 with the reference vessel diameter is inflated using the lowest pressure that will fully expand the balloon. This ensures that the stent will expand and helps to choose the stent size. If the patient experiences discomfort during balloon inflation, the inflation should be terminated and the lesion sizing reassessed. Pain may be caused by stretching of the adventitial layers of the vessel and may be a precursor to arterial rupture. Balloon-expandable stents, long enough to cover the lesion and sized 1:1 with the reference diameter, are used to scaffold the lesion and maximize the angiographic result.

Renal Artery Atherosclerotic Lesions

Atherosclerotic RAS usually involves the ostial and proximal portion of the main renal artery. These lesions are morphologically complex and can be difficult to visualize with two-dimensional angiography. The errors made with angiography are increased when interventionalists rely on “visual estimation” as the only means to determine lesion severity. Under the best of circumstances, visual estimation of angiographic stenoses lacks reproducibility and precision. Confirmation of the hemodynamic significance of moderate (50%–70%) renal artery stenosis is recommended by the guidelines and appropriate use documents.^{13,14} Late patency for renal stents is enhanced by optimally sizing stents, and IVUS enables operators to determine the reference vessel diameter much more accurately than angiographic assessment.

Atheroemboli are a concern with atherosclerotic lesions. Henry and coworkers¹⁵ placed renal stents in 65 renal arteries in 56 patients using embolic protection devices (EPDs). They noted debris retrieval after renal stent deployment in 100% of the patients with distal balloon occlusion and in 80% of the filter cases. Interestingly, there was no difference in the size or number of particles regardless of whether balloon predilation was performed or not. With the reported frequency of visible atherosclerotic debris recovered with EPDs

well above 50%, it is not surprising that 25% of successfully revascularized kidneys show a decline in renal function.¹

Fibromuscular Dysplasia

Fibromuscular dysplasia is commonly found in young adults with hypertension, especially women, but the condition can persist into later life.¹⁶ The angiographic appearance of a corrugated vessel is diagnostic of FMD. In a patient with FMD who has hypertension despite maximal medical therapy, balloon angioplasty alone is indicated, and the patient will usually respond to balloon angioplasty without the need for stenting. If the patient fails to respond to balloon angioplasty alone or if restenosis occurs, then renal stenting is a reasonable option.

Procedural Complications

Complications associated with catheter-based renal intervention are related to vascular access, catheter trauma, or systemic complications related to contrast reactions or renal toxicity. Vascular access complications are the most common complications in renal artery intervention. They include access site bleeding and hematoma (1.5%–5%), access site vessel injury (1%–2%), retroperitoneal hematoma (<1%), pseudoaneurysm (0.5%–1%), arteriovenous fistula, and nerve injury (<1%).¹ Major complications of peripheral vascular angiography range from 1.9% to 2.9% (Table 20.3).

Catheter-related renal artery complications include atheroembolism, vessel dissection, or arterial perforation, which are rare (<1%) but often devastating events. Anaphylactoid contrast reactions occur in fewer than 3% of cases, and less than 1% require hospitalization. The risk of contrast-induced nephropathy (CIN) is increased in patients with baseline chronic renal insufficiency, diabetes mellitus, and multiple myeloma and those who are receiving other nephrotoxic drugs such as aminoglycosides. Prevention of CIN requires vigorous hydration and the use of as little iso-osmolar contrast as possible.

Embolic Protection Devices

Embolic protection devices have been approved for clinical use in saphenous vein coronary bypass grafts and for cerebral protection during carotid stent placement. EPDs

are percutaneous devices that can be divided into three categories as follows: (1) filters, (2) distal occlusion balloons with aspiration of debris, and (3) proximal occlusion balloons with reversal of flow.

The aorto-ostial nature of most renal artery stenoses makes proximal occlusion devices unsuitable, which is why distal occlusion balloons and filters are the most common devices used in an off-label manner for renal protection. A single-center small randomized study of 100 patients compared four arms: (1) control, (2) EPD alone, (3) IIb/IIIa platelet receptor inhibitor alone, and (4) EPD + IIb/IIIa platelet receptor inhibitor.

The control group, EPD group, and IIb/IIIa platelet receptor inhibitor group demonstrated a decline in GFR ($P < .05$), but group 4 (combination therapy with EPD + IIb/IIIa platelet receptor inhibitor) did not have this decline, and results were superior to those of the other groups ($P < .01$). The main effects of treatment demonstrated no overall improvement in GFR; although the platelet receptor inhibitor was superior to placebo ($0 \pm 27\%$ vs $-10 \pm 20\%$; $P < .05$), embolic protection was not ($-1 \pm 28\%$ vs $-10 \pm 20\%$; $P < .08$). An interaction was observed between the platelet receptor inhibitor and embolic protection ($P < .05$), favoring combination treatment. The platelet receptor inhibitor reduced the occurrence of platelet-rich emboli in the filters from 42% to 7% ($P < .01$).¹⁷

Radial Artery Access

Vascular access complications account for the majority of bleeding complications of renal stenting. One way to minimize access site bleeding is to use the radial artery for access. The coronary interventional literature has demonstrated a marked reduction in vascular access complications with radial artery access compared with both brachial and femoral artery access. Low-profile radial sheaths and the ability to use a “sheathless” technique with 6-Fr guiding catheters make the radial artery approach a viable option (Figure 20.4).¹⁸ In addition to minimizing vascular access complications, the radial artery approach has other advantages, including increased patient acceptance and improved guiding catheter engagement because of the downward or caudal orientation of most renal arteries. The radial approach requires 125-cm guide catheters with 150-cm shaft length balloons and stents, and there is a

TABLE 20.3 Complications of Renal Stent Placement

REFERENCE	PATIENTS (n)	DEATH (%)	DIALYSIS (%)	MAJOR COMPLICATIONS (%)
Tuttle et al. ⁴²	148	0	0	4.1
Rocha-Singh et al. ²⁰	180	0.6	0	2.6
Burket et al. ⁴⁴	171	0	0.7	0.7
White et al. ¹¹	133	0	0	0.75
Dorros et al. ⁴⁵	163	0.6	0	1.8
TOTAL/MEAN	795	<1.0	<1.0	2.0

From Tuttle KR, Chouinard RF, Webber JT, et al. Treatment of atherosclerotic ostial renal artery stenosis with the intravascular stent. *Am J Kidney Dis*. 1998;32:611-622; Rocha-Singh KJ, Mishkel GJ, Katholi RE, et al. Clinical predictors of improved long-term blood pressure control after successful stenting of hypertensive patients with obstructive renal artery atherosclerosis. *Catheter Cardiovasc Interv*. 1999;47:167-172; Burket M, Cooper C, Kennedy D, et al. Renal artery angioplasty and stent placement: predictors of a favorable outcome. *Am Heart J*. 2000;139:64-71; White CJ, Ramee SR, Collins TJ, et al. Renal artery stent placement: utility in lesions difficult to treat with balloon angioplasty. *J Am Coll Cardiol*. 1997;30:1445-1450; and Dorros G, Jaff MR, Mathiak L, et al. Stent revascularization for atherosclerotic renal artery stenosis. 1-year clinical follow-up. *Tex Heart Inst J*. 1998;25:40-43.

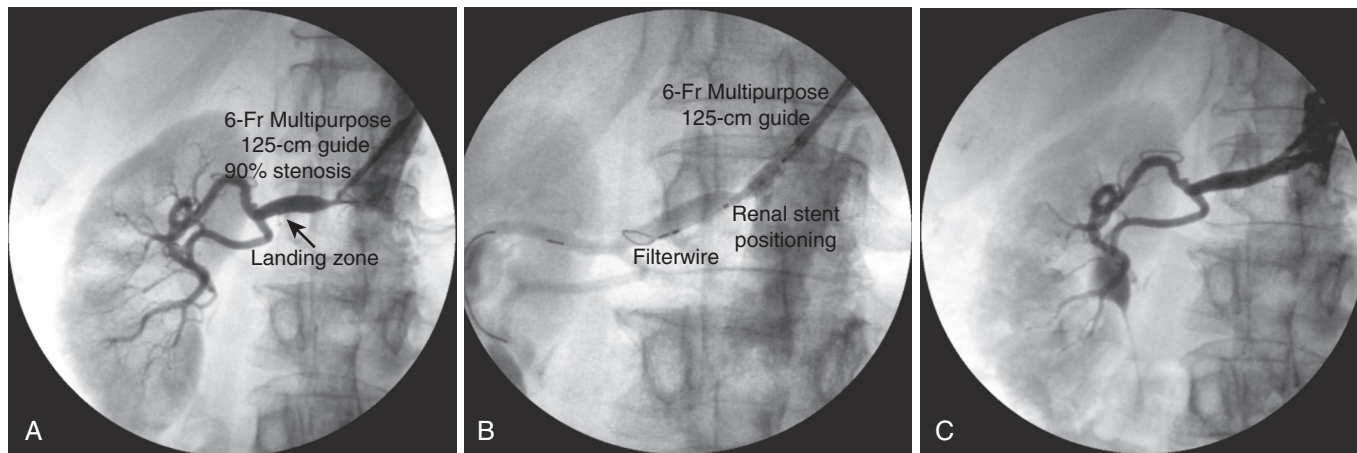


FIGURE 20.4 **A**, Baseline angiography using right radial artery access of a 90% stenosis of right renal artery using a 6-Fr multipurpose (125-cm) guide catheter. Note the landing zone (arrow) before the bifurcation, suitable for a filter device (off-label use). **B**, The filter device has been deployed, and the undeployed stent is being positioned across the lesion. **C**, Final angiogram after stent deployment and filter retrieval.

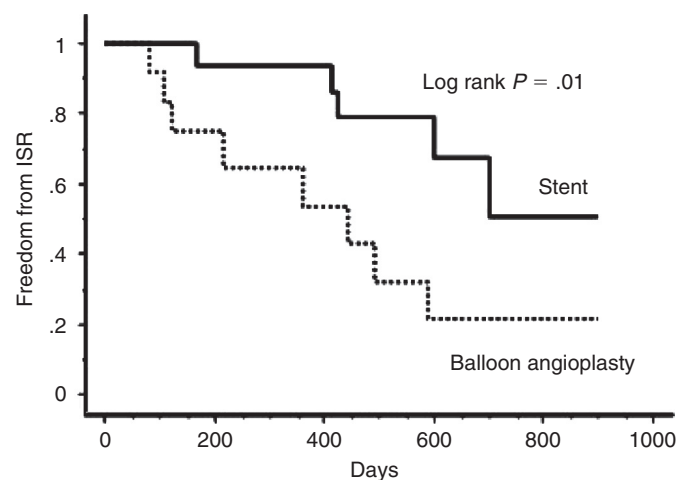


FIGURE 20.5 Kaplan-Meier curve comparing freedom from in-stent restenosis (ISR) for restenosis patients treated with a stent or balloon angioplasty.

minor learning curve. The undeniable benefit of the radial access approach, however, is a major reduction in vascular access-related complications with same-day discharge and increased patient satisfaction.

Renal Artery In-Stent Restenosis

The optimal treatment of renal artery in-stent restenosis is uncertain. Primary renal artery stent placement versus balloon angioplasty of in-stent restenosis lesions demonstrated improved patency for the stent arm with a 58% reduction in recurrent in-stent restenosis (29.4% vs 71.4%; $P = .02$) and a 30% reduction in follow-up diameter stenosis (41% vs 58.2%; $P = .03$) (Figure 20.5).¹⁹ The repeat stent group also had better secondary patency ($P = .05$) and a greater freedom from repeat in-stent restenosis ($P = .01$). Other methodologies such as coronary drug-eluting stents, covered stents, cutting balloons, and brachytherapy have been reported, but no systematic studies or any comparative data are available to support any strategy other than repeat bare-metal stenting.

ASYMPTOMATIC RENAL ARTERY STENOSIS

There is no evidence to support beneficial outcomes for revascularization of an asymptomatic renal artery stenosis, regardless of the severity of the stenosis. The current American College of Cardiology/American Heart Association (ACC/AHA) guidelines make renal intervention for unilateral asymptomatic, bilateral asymptomatic, or solitary asymptomatic RAS a Class lib, level of evidence (LOE) C recommendation that suggests there is an uncertain risk-to-benefit ratio for this treatment.² Patients with compelling anatomic lesions, threatening global renal function, may be considered for treatment on a case-by-case basis.

RENOVASCULAR HYPERTENSION

Clinical Characteristics

It has been shown that patients with the highest systolic blood pressures (SBPs) have the greatest decrease in SBP after renal stenting, but there is no correlation between blood pressure improvement after renal stent placement and the variables of age, sex, race, severity of stenosis, number of vessels treated, baseline diastolic blood pressure (DBP), or baseline serum creatinine. Two variables, bilateral renal artery stenosis (odds ratio [OR], 4.6; $P = .009$) and mean arterial pressure greater than 110 mm Hg (OR, 2.9; $P = .003$), are associated with improved blood pressure response after renal artery stent placement.²⁰ Studies comparing the results in older adults (75 years and older) versus younger (younger than 75 years) patients or in women versus men have failed to show any difference in response to renal stent placement.

An analysis of 72 patients with resistant hypertension defined by daytime ambulatory blood pressure measurement (dABP) greater than 135 mm Hg systolic and 85 mm Hg diastolic despite therapy with at least three antihypertensive drugs (mean, 4.0 ± 1) including a full-dose diuretic, found benefit for renal stenting.²¹ Follow-up measurements using dABP decreased from $157 \pm 16/82 \pm 10$ mm Hg to

$143 \pm 17/75 \pm 10$ mm Hg ($P < .001$) even as antihypertensive drug requirements declined. These changes persisted in the cohorts followed with repeat ABPM at 1 year and later at a median of 3.3 years after revascularization. The average decrease in dABP was 14/6 mm Hg, but more than 61% achieved at least a 10-mm Hg SBP reduction, and 39% achieved a greater than 20-mm Hg reduction, and 34% achieved goal blood pressure lower than 135/85 mm Hg. The likelihood of achieving goal blood pressure was related to younger age, lower initial SBP, lower body mass index, and higher estimated GFR class.

Prevalence

The prevalence of atherosclerotic renal artery stenosis depends on the population examined. In an outpatient Medicare population (mean age, 77 years), screening renal duplex ultrasonography studies demonstrated 60% or greater stenosis in 6.8%.²² There were almost twice as many men (9.1%) as women (5.5%; $P = .053$), and there were no racial differences (white patients, 6.9%; African American patients, 6.7%) in the prevalence of renal artery stenosis. Among the general hypertensive population, renal artery stenosis is the most common (2%–5%) secondary cause of hypertension. An autopsy series of patients aged older than 50 years found renal artery stenosis in 27%, increasing to 53% if there was a history of diastolic hypertension. Among patients entering dialysis treatment, 10% to 15% have renal artery stenosis as the cause of their end-stage renal disease.²³ Approximately 25% of older adult patients with unexplained chronic kidney disease have unsuspected renal artery stenosis.

Epidemiology

Renal artery stenosis is predominantly caused by atherosclerosis in the adult population, with FMD (Figure 20.6) being more common in younger women.¹⁶ RAS is more common in patients who have atherosclerosis involving

any other vascular bed. In patients undergoing cardiac catheterization for suspected coronary artery disease, the prevalence of RAS ranges from 25% to 30%, and peripheral arterial disease or abdominal aortic aneurysm is associated with renal artery stenosis in 30% to 40%.²

EVIDENCE-BASED TREATMENT

Recently data from 527 patients enrolled in five modern prospective, multicenter (117 centers), industry-sponsored, US Food and Drug Administration investigational device exemption (IDE)-approved studies were combined into a database, and a pooled analysis was performed.²⁴ After renal stenting, SBP and DBP were significantly decreased at 9 months. An SBP reduction greater than 10 mm Hg occurred in 61% of patients. A baseline SBP greater than 150 mm Hg was strongly associated with blood pressure response, but other clinical characteristics were not. In patients with hypertension in whom renal artery stenosis is identified, the only reliable predictor of benefit is SBP greater than 150 mm Hg before the procedure.

The current ACC/AHA guideline² indications for RAS in hypertensive patients with hemodynamically significant RAS and a viable kidney (linear length >7 cm) include the following:

- Accelerated hypertension
- Refractory hypertension (failure of three appropriate drugs, one of which should be a diuretic)
- Hypertension with a small kidney
- Hypertension with intolerance to medications (Class I, LOE B)

By convention, a hemodynamically significant lesion requires demonstration of a 70% or greater RAS by visual estimation, 70% or greater RAS by IVUS measurement, or a 50% to 70% RAS with a systolic (hyperemic) gradient of 20 mm Hg or greater, renal fractional flow reserve of 0.8 or less, or a mean translesional gradient of 0 mm Hg or greater.^{2,13,14}

The CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial compared the initial treatment strategy for patients with renovascular hypertension between multifactorial GDMT (e.g., an angiotensin receptor blocking agent, a thiazide-type diuretic, amlodipine, atorvastatin, antiplatelet therapy, and diabetes managed according to clinical practice guidelines) with GDMT plus renal stenting.²⁵ The CORAL study found that the primary composite endpoint (death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive failure, progressive renal insufficiency, or the need for renal replacement therapy) in patients with renal artery stenosis ($>60\%$ diameter stenosis) and poorly controlled hypertension taking at least two or more medications did not differ between groups. The number of blood pressure medications did not differ between the groups (medical, 3.5 ± 1.4 vs stent, 3.3 ± 1.5) at the completion of the trial, and both groups had a similar fall in SBP, 15.6 mm Hg $\pm$ 25.8 mm Hg in the medical therapy group and 16.6 mm Hg $\pm$ 21.2 mm Hg in the stent group.

In a subsequent analysis of the CORAL data, the authors found that patients with proteinuria had significantly worse outcomes than those without.²⁶ When baseline

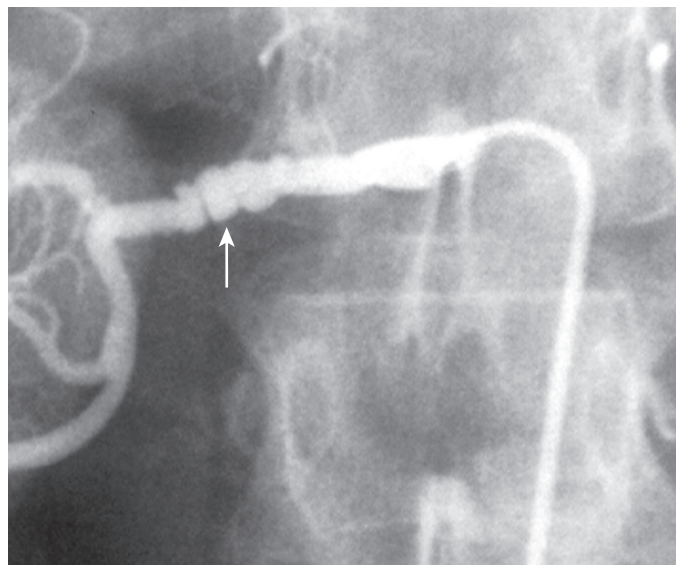


FIGURE 20.6 Angiography of the classic string of pearls sign (arrow) of renal fibromuscular dysplasia.



urine albumin-to-creatinine ratio was 22.5 mg/g or less, RAS was associated with significantly better event-free survival from the primary composite endpoint (73% vs 59% at 5 years; $P = .02$), cardiovascular disease-related death (93% vs 85%; $P \leq .01$), progressive renal insufficiency (91% vs 77%; $P = .03$), and overall survival (89% vs 76%; $P \leq .01$).

The CORAL recommendations for an initial trial of multifactorial GDMT is consistent with the current ACC/AHA guidelines, which require that patients fail GDMT for renovascular hypertension before consideration for revascularization.^{2,13,14}

ISCHEMIC NEPHROPATHY

Prevalence

Ischemic nephropathy, its incidence, and its reversibility continue to be sources of debate among experts.²⁷ The number of patients with atherosclerotic RAS requiring dialysis therapy is increasing. Opponents of aggressive revascularization of RAS patients with renal insufficiency contend that the kidney is supplied with an excess of nutrient blood flow, and therefore few kidneys will benefit from revascularization.

Evidence-Based Treatment

The literature is replete with patient series in which RAS improves renal function²⁸ as well as counterbalancing reports of worsening of renal failure after successful RAS.²⁹ However, there have been no large randomized studies demonstrating the benefit of revascularization over GDMT alone for improving renal function.

Unfortunately, there have been several poorly done studies such as the recently completed STAR (Stent placement and blood pressure and lipid-lowering for the prevention of progression of renal dysfunction caused by Atherosclerotic ostial stenosis of the Renal artery) trial³⁰ and the ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) trial comparing RAS plus GDMT with GDMT alone.³¹ Unfortunately, methodologic problems, such as enrolling study patients with mild (<50%) or nonobstructive RAS, weakened these “intention-to-treat” trials. The sweeping negative statements regarding the efficacy of RAS were not supported by the evidence presented.

Dramatic benefit for RAS versus GDMT in the patients with the most severe renal disease was demonstrated in a large cohort study.³² One center offered patients ($n = 182$) GDMT only, and the other center offered RAS plus GDMT ($n = 348$). Patients were matched for the degree of renal dysfunction, and outcomes were compared over 5 years. Patients who underwent RAS had a marked reduction in mortality (relative risk, 0.55; 95% confidence interval, 0.34–0.88); $P = .013$ by multivariate Cox regression analysis. When analyzed according to the degree of renal impairment, there were striking improvements in renal function after RAS for the patients with moderate to severe renal impairment. The authors concluded that patients with RAS and advanced chronic kidney disease (stages 4 and 5) benefit from RAS with improved renal function and enjoyed a survival advantage.

Currently, several parameters suggest that a patient is likely to have improved renal function after revascularization. First, there must be an obstructive renal artery stenosis lesion causing hypoperfusion of the kidney. The more renal tissue at risk, the more likely there will be a response or improvement with stenting. Patients with bilateral renal stenosis and solitary kidney stenosis are traditionally thought to be most likely to improve. Last, patients with small kidneys (<7 cm) and those with significant proteinuria are less likely to benefit.²⁶

Patients with rapidly declining renal function, as opposed to those with stable renal failure, have the most to gain from revascularization.²⁸ The rate of decline in renal function, determined by the slope of the regression line of serum creatinine over time, is a very strong predictor of benefit with stenting. A multivariate analysis demonstrated the only significant predictor of benefit after stenting was the rate of decline of renal function that preceded the procedure. Baseline creatinine, the presence of proteinuria, renal size, and diabetes were not significant predictors of improvement in this study.

The current ACC/AHA guideline recommendation² for catheter-based therapy to preserve renal function concludes that stenting is reasonable for patients with significant RAS and progressive chronic kidney disease with bilateral RAS or a solitary functioning kidney with stenosis (Class Iia, LOE B). Renal stenting may also be considered on an individual basis for patients with hemodynamically significant stenosis and chronic renal insufficiency with unilateral RAS (Class Iib, LOE C).

CARDIAC DESTABILIZATION SYNDROMES

Cardiac destabilization syndromes attributable to renal artery stenosis include exacerbations of coronary ischemia and congestive heart failure (CHF) caused by peripheral arterial vasoconstriction or volume overload.² Renovascular disease may also complicate the management of patients with heart failure by preventing administration of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.

Flash pulmonary edema associated with significant RAS (Pickering syndrome) is an accepted indication for renal stenting.³³ In a review of 87 cases, there was improvement in renal function in 81%, and there was no recurrence of pulmonary edema in 92%.

The importance of renal artery stent placement in the treatment of cardiac disturbance has been described in a series of patients presenting with either CHF or an acute coronary syndrome.³⁴ Successful renal stent placement resulted in a significant decrease in blood pressure and control of symptoms in 88% (42 of 48) of all patients. Assessment of the treatment effects acutely and at 8 months using the Canadian Cardiovascular Society angina classification (Figure 20.7) and the New York Heart Association functional classification (Figure 20.8) were not different between the combined coronary and renal revascularization group compared with those who had only renal stent placement, suggesting that renal revascularization was the most significant intervention.

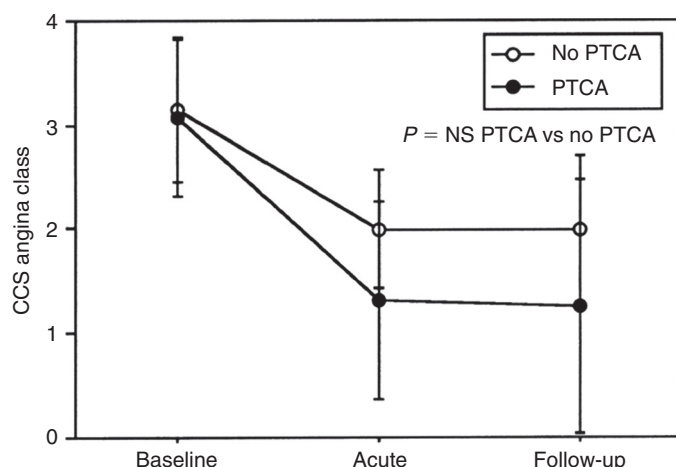


FIGURE 20.7 Effect of renal artery stent implantation with percutaneous transluminal coronary angioplasty (PTCA) (group I, $n = 13$) and without PTCA (group II, $n = 7$) on Canadian Cardiovascular Society (CCS) angina class in patients presenting with unstable angina. NS, Not significant. (Reprinted with permission from Khosla S, White CJ, Collins TJ, et al. Effects of renal artery stent implantation in patients with renovascular hypertension presenting with unstable angina or congestive heart failure. *Am J Cardiol.* 1997;80(3):363-366.)

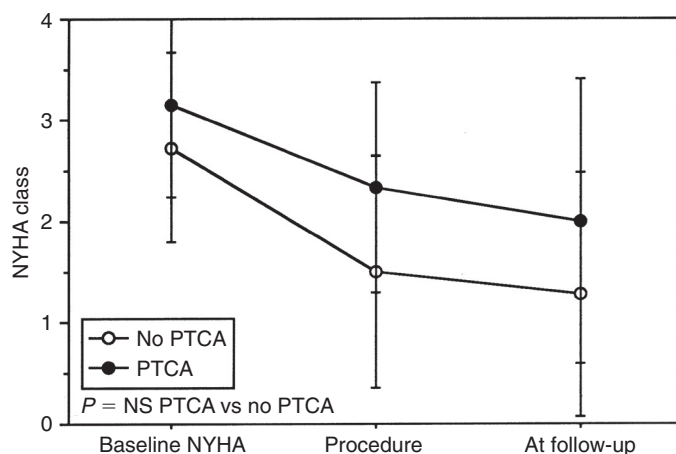


FIGURE 20.8 Effect of renal artery stent implantation with percutaneous transluminal coronary angioplasty (PTCA) (group III, $n = 28$) or without PTCA (group IV, $n = 6$) on New York Heart Association (NYHA) functional class of patients presenting with congestive heart failure. NS, Not significant. (Reprinted with permission from Khosla S, White CJ, Collins TJ, et al. Effects of renal artery stent implantation in patients with renovascular hypertension presenting with unstable angina or congestive heart failure. *Am J Cardiol.* 1997;80(3):363-366.)

A case series of 39 patients treated with renal artery stent implantation to control CHF demonstrated blood pressure improved in 72% of patients; renal function improved in 51% and was stable in 26% of patients.³⁵ The mean number of hospitalizations for CHF before stenting was 2.37 ± 1.42 (range, 1–6) and after renal stenting was 0.30 ± 0.065 (range, 0–3) ($P < .001$). Seventy-seven percent of patients had no further hospitalizations after treatment for RAS over a mean follow-up period of 21.3 months.

Percutaneous therapy can relieve the RAS and result in marked improvement in both heart failure and angina symptoms. The ACC/AHA guidelines make percutaneous revascularization for hemodynamically significant RAS and recurrent, unexplained CHF or sudden unexplained pulmonary edema a Class I, LOE B indication. RAS for renal artery stenosis and refractory unstable angina earned a Class Iia, LOE B indication.²

SUMMARY

Patients with presumed atherosclerotic renovascular hypertension should initially be given a trial of GDMT to treat their blood pressure. For patients whose blood pressure is not controlled with GDMT or who cannot tolerate medical therapy, one should follow the recommendation of the guidelines and appropriate use documents, which state that it is reasonable to offer RAS to patients with an atherosclerotic severe renal artery stenosis ($>70\%$ angiographic diameter renal artery stenosis or 50% – 70% stenosis with hemodynamic confirmation of lesion severity).^{2,13,14}

Catheter-based therapy for symptomatic (refractory hypertension, progressive ischemic nephropathy, or cardiac destabilization syndromes), hemodynamically significant, atherosclerotic RAS is the preferred method of revascularization. The discordance between the high ($>95\%$) procedural success and the moderate (60% – 70%) clinical response is most likely due to three major factors: poor patient selection, poor discrimination of lesion severity by angiography, and the coexistence of severe parenchymal renal disease (proteinuria). Encouraging data suggest that the use of physiologic lesion assessment can enhance selection for revascularization and improve clinical response rates.^{13,14} In addition to maximizing the clinical benefit by better patient and lesion selection for RAS, the broader use of radial artery access for renal stenting will decrease vascular access complications, improve patient satisfaction, and enable same-day discharge in a subset of the patients.

REFERENCES

- Prince M, Tafur JD, White CJ. When and how should we revascularize patients with atherosclerotic renal artery stenosis? *JACC Cardiovasc Interv.* 2019;12:505-517.
- Anderson JL, Halperin JL, et al. Management of patients with peripheral artery disease (Compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127(13):1425-1443.
- White CJ, Jaff MR, Haskal ZJ, et al. Indications for renal arteriography at the time of coronary arteriography: a science advisory from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology, and the Councils on Cardiovascular Radiology and Intervention and on Kidney in Cardiovascular Disease. *Circulation.* 2006;114:1892-1895.
- Harvin HJ, Verma N, Nikolaidis P, et al. ACR Appropriateness criteria renovascular hypertension. *J Am Coll Radiol.* 2017;14(suppl):S540-S549.
- Mohler III ER, Gornik HL, Gerhard-Herman MD, et al. ACCF/ACR/AIUM/ASE/ASN/ICAVL/SCAI/SCCT/SIR/SVM/SVS 2012 appropriate use criteria for peripheral vascular ultrasound and physiological testing part I: arterial ultrasound and physiological testing. *J Am Coll Cardiol.* 2012;60:242-276.
- Del Conde I, Galin ID, Trost B, et al. Renal artery duplex ultrasound criteria for the detection of significant in-stent restenosis. *Catheter Cardiovasc Interv.* 2013;83:612-618.
- Zeller T, Frank U, Muller C, et al. Predictors of improved renal function after percutaneous stent-supported angioplasty of severe atherosclerotic ostial renal artery stenosis. *Circulation.* 2003;108:2244-2249.
- Subramanian R, White CJ, Rosenfield K, et al. Renal fractional flow reserve: a hemodynamic evaluation of moderate renal artery stenoses. *Catheter Cardiovasc Interv.* 2005;64:480-486.
- Van Brussel PM, Van de Hoef TP, De Winter RJ, et al. Hemodynamic measurements for the selection of patients with renal artery stenosis. *JACC Cardiovasc Interv.* 2017;10:973-985.
- De Bruyne B, Manoharan G, Pijls NH, et al. Assessment of renal artery stenosis severity by pressure gradient measurements. *J Am Coll Cardiol.* 2006;48:1851-1855.
- White CJ, Ramee SR, Collins TJ, et al. Renal artery stent placement: utility in lesions difficult to treat with balloon angioplasty. *J Am Coll Cardiol.* 1997;30:1445-1450.
- Lederman R, Mendelsohn F, Santos R, et al. Primary renal artery stenting: characteristics and outcomes after 363 procedure. *Am Heart J.* 2001;142:314-323.

13. Bailey SR, Beckman JA, Dao TD, et al. ACC/AHA/SCAI/SIR/SVM 2018 Appropriate Use Criteria for Peripheral Artery Intervention: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Heart Association, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2019;73:214-237.
14. Klein AJ, Jaff MR, Gray BH, et al. SCAI appropriate use criteria for peripheral arterial interventions: an update. *Catheter Cardiovasc Interv*. 2017;90:E90-E110.
15. Henry M, Klonaris C, Henry I, et al. Protected renal stenting with the Percu-Surge GuardWire device: a pilot study. *J Endovasc Ther*. 2001;8:227-237.
16. Slovut DP, Olin JW. Fibromuscular dysplasia. *N Engl J Med*. 2004;350:1862-1871.
17. Cooper C, Haller S, Colyer W, et al. Embolic protection and platelet inhibition during renal artery stenting. *Circulation*. 2008;117:2752-2760.
18. Trani C, Tommasino A, Burzotta F. Transradial renal stenting: why and how. *Catheter Cardiovasc Interv*. 2009;74:951-956.
19. N'Dandu ZM, Badawi RA, White CJ, et al. Optimal treatment of renal artery in-stent restenosis: repeat stent placement versus angioplasty alone. *Catheter Cardiovasc Interv*. 2008;71:701-705.
20. Rocha-Singh KJ, Mishkel GJ, Katholi RE, et al. Clinical predictors of improved long-term blood pressure control after successful stenting of hypertensive patients with obstructive renal artery atherosclerosis. *Catheter Cardiovasc Interv*. 1999;47:167-172.
21. Courand PY, Dinic M, Lorthioir A, et al. Resistant hypertension and atherosclerotic renal artery stenosis: effects of angioplasty on ambulatory blood pressure. A retrospective uncontrolled single-center study. *Hypertension*. 2019;74:1516-1523.
22. Hansen KJ, Edwards MS, Craven TE, et al. Prevalence of renovascular disease in the elderly: a population-based study. *J Vasc Surg*. 2002;36:443-451.
23. Guo H, Kalra PA, Gilbertson DT, et al. Atherosclerotic renovascular disease in older US patients starting dialysis, 1996 to 2001. *Circulation*. 2007;115:50-58.
24. Weinberg I, Keyes MJ, Giri J, et al. Blood pressure response to renal artery stenting in 901 patients from five prospective multicenter FDA-approved trials. *Catheter Cardiovasc Interv*. 2014;83:603-609.
25. Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med*. 2014;370:13-22.
26. Murphy TP, Cooper CJ, Pencina KM, et al. Relationship of Albuminuria and renal artery stent outcomes. *Hypertension*. 2016;68:1145-1152.
27. Textor SC, Lerman L, McKusick M. The uncertain value of renal artery interventions: where are we now? *JACC Cardiovasc Interv*. 2009;2:175-182.
28. Muray S, Martin M, Amoedo M, et al. Rapid decline in renal function reflects reversibility and predicts the outcome after angioplasty in renal artery stenosis. *Am J Kidney Dis*. 2002;39:60-66.
29. DeJani H, Eisen TD, Finkelstein FO. Revascularization of renal artery stenosis in patients with renal insufficiency. *Am J Kidney Dis*. 2000;36:752-758.
30. Bax L, Woittiez AJ, Kouwenberg HJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann Intern Med*. 2009;150:840-848.
31. Wheatley K, Ives N, Gray R, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361:1953-1962.
32. Kalra PA, Chrysoschou C, Green D, et al. The benefit of renal artery stenting in patients with atheromatous renovascular disease and advanced chronic kidney disease. *Catheter Cardiovasc Interv*. 2010;75:1-10.
33. Messerli FH, Bangalore S, Makani H, et al. Flash pulmonary oedema and bilateral renal artery stenosis: the Pickering syndrome. *Eur Heart J*. 2011;32(18):2231-2235.
34. Khosla S, White CJ, Collins TJ, et al. Effects of renal artery stent implantation in patients with renovascular hypertension presenting with unstable angina or congestive heart failure. *Am J Cardiol*. 1997;80:363-366.
35. Gray BH, Olin JW, Childs MB, et al. Clinical benefit of renal artery angioplasty with stenting for the control of recurrent and refractory congestive heart failure. *Vasc Med*. 2002;7:275-279.
36. Boisclair C, Therasse E, Oliva VL, et al. Treatment of renal angioplasty failure by percutaneous renal artery stenting with Palmaz stents: midterm technical and clinical results. *AJR Am J Roentgenol*. 1997;168:245-251.
37. Blum U, Krumme B, Flugel P, et al. Treatment of ostial renal-artery stenoses with vascular endoprostheses after unsuccessful balloon angioplasty [see comments]. *N Engl J Med*. 1997;336:459-465.
38. Henry M, Amor M, Henry I, et al. Stent placement in the renal artery: three-year experience with the Palmaz stent. *J Vasc Interv Radiol*. 1996;7:343-350.
39. Rees CR, Palmaz JC, Becker GJ, et al. Palmaz stent in atherosclerotic stenoses involving the ostia of the renal arteries: preliminary report of a multicenter study. *Radiology*. 1991;181:507-514.
40. Kuhn FP, Kutkuhn B, Torsello G, et al. Renal artery stenosis: preliminary results of treatment with the Strecker stent. *Radiology*. 1991;180:367-372.
41. Wilms GE, Peene PT, Baert AL, et al. Renal artery stent placement with use of the Wallstent endoprosthesis. *Radiology*. 1991;179:457-462.
42. Tuttle KR, Chouinard RF, Webber JT, et al. Treatment of atherosclerotic ostial renal artery stenosis with the intravascular stent. *Am J Kidney Dis*. 1998;32:611-622.
43. Van de Ven PJ, Kaatee R, Beutler JJ, et al. Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. *Lancet*. 1999;353:282-286.
44. Burket M, Cooper C, Kennedy D, et al. Renal artery angioplasty and stent placement: predictors of a favorable outcome. *Am Heart J*. 2000;139:64-71.
45. Dorros G, Jaff MR, Mathiak L, et al. Stent revascularization for atherosclerotic renal artery stenosis. 1-year clinical follow-up. *Tex Heart Inst J*. 1998;25:40-43.



21

Mesenteric Artery Intervention: Catheter-Based Therapy For Chronic Mesenteric Ischemia

CHRISTOPHER J. WHITE

INTRODUCTION, 381

Prevalence, 381

Cause, 381

Natural History, 381

DIAGNOSIS, 381

Clinical Presentation, 381

Imaging, 381

MANAGEMENT OF CHRONIC

MESENTERIC ISCHEMIA, 382

Medical Therapy, 382

Catheter-Based Endovascular

Therapy, 382

Surgical Therapy, 383

Postprocedure Management and

Follow-up, 383

CONCLUSIONS, 383

INTRODUCTION

Prevalence

The prevalence of asymptomatic mesenteric arterial stenoses is much more common than the relatively uncommon clinical syndrome of chronic mesenteric ischemia (CMI).¹ This is because of the rich vascular communication among the three mesenteric vessels, the celiac artery (CA), superior mesenteric artery (SMA), and inferior mesenteric artery (IMA). CMI is twice as common in women than men and in a healthy group of older adults (older than 65 years), ultrasound imaging found a 17.5% prevalence of asymptomatic (>70%) stenosis of at least one mesenteric artery.^{1,2} As with other predominantly atherosclerotic vascular diseases, the prevalence increases with advancing age.^{1,2}

Cause

Classical teaching suggests that CMI occurs when only one of three mesenteric arteries (CA, SMA, and IMA) remains patent because of the rich collateral supply, and the most commonly intervened on vessel is the SMA. Causes of CMI include vascular conditions such as fibromuscular dysplasia, Takayasu's disease, Buerger's disease, radiation and autoimmune arteritis, and aortic dissection, but atherosclerosis is the predominant (>95%) cause of clinical mesenteric arterial stenosis.²

Natural History

The natural history of asymptomatic mesenteric artery stenosis is benign in that clinical symptoms develop in a minority (<6%) of patients over 6 years.² For patients with symptomatic CMI, between 20% to 50% of patients develop acute mesenteric ischemia. The remaining patients continue to have chronic postprandial abdominal pain, weight loss, and emaciation.

DIAGNOSIS

Clinical Presentation

The classical symptoms of CMI include abdominal discomfort triggered by food ingestion accompanied by unexplained weight loss (Table 21.1). The abdominal pain is often periumbilical and described as dull aching or sometimes as “crampy” and begins within 1 hour after food ingestion and subsides 1 to 2 hours later. Many patients develop a “fear of food” and decrease their caloric intake, resulting in unintended weight loss. Significant weight loss often helps to differentiate patients with functional bowel symptoms from those with CMI.

Ischemic gastropathy, ischemic colitis, and malabsorption are less common manifestations of CMI. Ischemic gastropathy usually manifests as nausea, vomiting, fullness, right upper quadrant discomfort, abdominal pain, and weight loss. Ischemic colitis presents with abdominal pain, gastrointestinal bleeding, or hematochezia.² The diagnosis may be delayed because patients may be referred for a malignancy evaluation for weight loss. However, evidence of significant stenosis of two or more mesenteric vessels in conjunction with endoscopic findings of bowel ischemia should prompt the diagnosis. CMI may occur in single-vessel mesenteric artery disease, particularly after abdominal surgery if mesenteric collaterals have been disrupted. Because of the difficulty in making this diagnosis, a multidisciplinary team approach is encouraged.

Imaging

Doppler ultrasonography (duplex) is the preferred screening test for mesenteric artery stenosis. Noninvasive cross-sectional imaging with computed tomography angiography and magnetic resonance angiography can establish the presence of mesenteric arterial stenosis.^{1,2}

TABLE 21.1 Most Frequent Symptoms of Chronic Mesenteric Ischemia

SYMPTOMS	RATE (%)
Typical Symptoms	78%
Postprandial abdominal pain	
Fear of food	
Weight loss (>20 lb)	
Ischemic Gastropathy	14%
Nausea and vomiting	
Fullness	
Abdominal pain	
Right upper quadrant discomfort	
Weight loss	
Ischemic Colitis	8%
Abdominal pain	
Gastrointestinal bleeding	
Hematochezia	

Invasive angiography remains the gold standard for visualizing the mesenteric arterial tree. Visualization of the mesenteric vessels requires a lateral aortogram ([Figure 21.1](#)). The anteroposterior aortogram may reveal the arc of Rioloan, an engorged collateral connecting the IMA to the SMA and indicative of proximal mesenteric artery disease.

MANAGEMENT OF CHRONIC MESENTERIC ISCHEMIA

Medical Therapy

Patients with asymptomatic CMI should be treated with antiatherosclerotic guideline-directed medical therapy, including lipid-lowering therapy with a statin, smoking cessation, blood pressure control, diabetes control, and antiplatelet therapy.³⁻⁵ Treatment with digoxin should be avoided because of the detrimental actions of digoxin in the splanchnic circulation, causing vasoconstriction and ischemia.

Current guideline recommendations are that patients with symptomatic CMI should be evaluated for revascularization.³⁻⁵ Without revascularization, they risk progression

of their disease and the development of acute mesenteric ischemia, inanition, and death.

Catheter-Based Endovascular Therapy

Catheter-based endovascular revascularization techniques are preferred to open surgery because of their lower procedural morbidity and mortality rates, shorter length of stay, and earlier recovery.⁶ Endovascular therapies may be repeated if necessary, generally without increased patient risk compared with the first procedure, and prior angioplasty does not preclude surgery if required at a later date. The number of endovascular procedures performed for CMI in the United States has increased significantly over the past 2 decades.⁷

The aorto-ostial location of the stenoses, as is the case for renal artery stenoses, is the most common cause of CMI and is difficult to treat with balloon angioplasty alone because of elastic recoil. Scaffolding the lesion with a stent defeats this recoil, resulting in a larger lumen diameter and higher procedural success rate than for balloon dilation alone ([Figure 21.2](#)) and ([Videos 21.1](#) and [21.2](#)).

A large prospective population-based national registry study from Denmark reported on endovascular therapy in 178 patients with CMI over a 5-year period.⁶ The 30-day mortality rate was 1.7% with a 1-year survival rate of 85% and a 3-year survival rate of 74%. At discharge, 85% of patients were clinically improved with 1-year continued improvement in 78.6%. Clinically driven target lesion revascularization occurred in 7.3% at 1 year. Periprocedural complications occurred in 10 (5.6%) patients, including brachial artery access site bleeding ($n = 1$) or thrombosis ($n = 3$), femoral artery thrombosis ($n = 1$), target vessel embolization ($n = 1$), and target vessel thrombosis or dissection ($n = 4$).

In an attempt to improve patency rate of mesenteric artery intervention, a nonrandomized case series compared balloon-expandable covered stents with bare-metal stents (BMSs) in 225 patients and found a significant reduction in

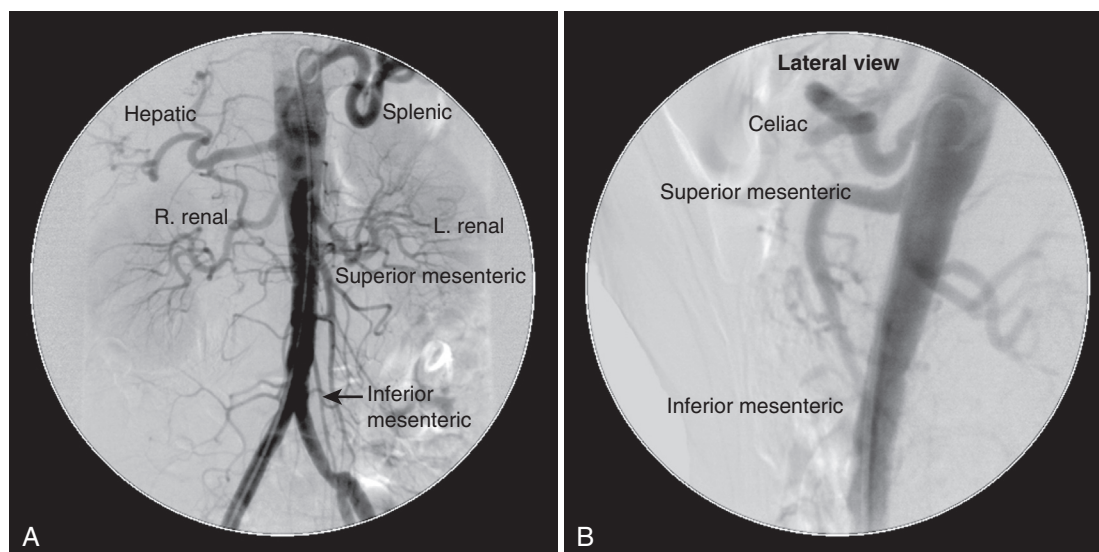


FIGURE 21.1 **A**, Anteroposterior abdominal aortic angiogram showing branches. **B**, Lateral abdominal aortic angiogram showing mesenteric branches. L, Left; R, right.

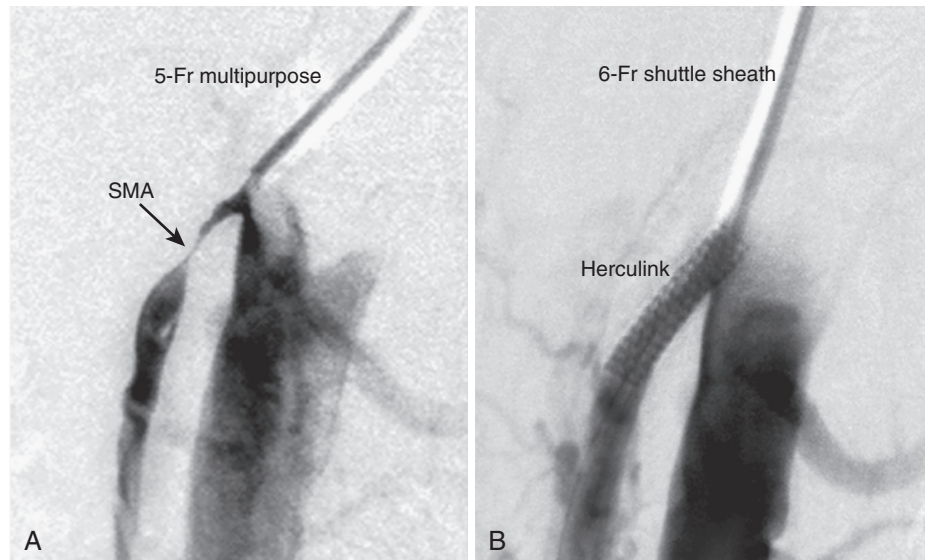


FIGURE 21.2 **A**, Baseline lateral angiogram of tight superior mesenteric artery (SMA) stenosis. **B**, Angiogram after successful balloon-expandable stent placement.

restenosis with covered stents, with no increased risk of stent thrombosis.⁸ At a mean follow-up period of 29 ± 12 months, patients treated with covered stents had higher freedom from symptom recurrence ($92 \pm 4\%$ vs $50 \pm 5\%$; $P < .003$) and higher primary patency at 3 years ($92\% \pm 6\%$ vs $52\% \pm 5\%$; $P < .003$) compared with those treated with BMSs.

Surgical Therapy

No clinical trials have directly compared surgical versus catheter-based revascularization strategies for patients with CMI. Traditionally, revascularization for CMI has been performed via open surgery with either endarterectomy or bypass grafting. Because patients with CMI have systemic atherosclerosis and are malnourished, they frequently have an increased risk for surgical complications, and the perioperative surgical mortality rate ranges from 3.5% to 15%.⁹

Whether patients who survive surgery have higher patency rates and symptom-free survival rates than patients treated with stent revascularization is controversial.¹⁰ Data from the Mayo Clinic on 229 consecutive patients with CMI demonstrated that surgical patients had greater morbidity and longer hospitalization than the endovascular group, with a higher restenosis rate for endovascular therapy, but there was no difference in secondary patency between surgery and stented patients.¹¹

Using an administrative database (2007–2014 National Inpatient Sample), propensity-matched cohorts were used to compare outcomes between open surgery and endovascular therapy.⁷ Endovascular therapy resulted in significantly fewer major adverse cardiac and cerebral events (8.6% vs 15.9%; $P < .001$), with lower costs and shorter hospital stays (Figure 21.3).

Postprocedure Management and Follow-Up

Because revascularization treatment is symptom driven, routine follow-up with mesenteric artery Doppler ultrasonography (duplex) is not advisable to evaluate continued

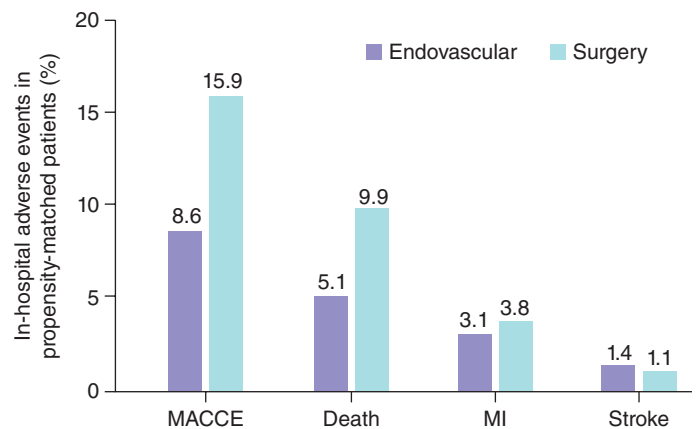


FIGURE 21.3 Bar graph of in-hospital adverse event rates in propensity matched patients for surgery and endovascular treatment of chronic mesenteric ischemia. MACCE, Major adverse cardiac and cerebral event; MI, myocardial infarction. (From Lima FV, Kolte D, Kennedy KF, et al. Endovascular versus surgical revascularization for chronic mesenteric ischemia: insights from the National Inpatient Sample database. *JACC Cardiovasc Interv.* 2017;10:2440-2447.)

patency. Any recurrence of symptoms (e.g., postprandial pain or unintended weight loss) should prompt investigation for recurrent stenosis.

CONCLUSIONS

The infrequent occurrence of CMI has made randomized controlled trials comparing treatment outcomes very difficult to perform. Asymptomatic patients with mesenteric artery stenosis should receive guideline-directed antiatherosclerotic medical therapy. Case series have shown that percutaneous therapy with stent placement offers the lowest morbidity and roughly equivalent long-term outcomes compared with surgery. The current treatment recommendation is that patients who are candidates for either surgery or percutaneous therapy should receive percutaneous therapy with primary stent placement.



REFERENCES

1. Sardar P, White CJ. Chronic mesenteric ischemia: diagnosis and management. *Prog Cardiovasc Dis*. 2021;65:71-75.
2. Kolkman JJ, Geelkerken RH. Diagnosis and treatment of chronic mesenteric ischemia: an update. *Best Pract Res Clin Gastroenterol*. 2017;31:49-57.
3. Hirsch AT, Haskal ZJ, Hertzner NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *J Am Coll Cardiol*. 2006;47:1239-1312.
4. Huber TS, Björck M, Chandra A, et al. Chronic mesenteric ischemia: clinical practice guidelines from the Society for Vascular Surgery. *J Vasc Surg*. 2021;73(suppl):87S-115S.
5. Pillai AK, Kalva SP, Hsu SL, Society of Interventional Radiology Standards of Practice Committee, et al. Quality Improvement Guidelines for Mesenteric Angioplasty and Stent Placement for the Treatment of Chronic Mesenteric Ischemia. *J Vasc Interv Radiol*. 2018;29:642-647.
6. Altintas Ü, Lawaetz M, de la Motte L, et al. Endovascular treatment of chronic and acute on chronic mesenteric ischaemia: results from a national cohort of 245 cases. *Eur J Vasc Endovasc Surg*. 2021;61:603-611.
7. Lima FV, Kolte D, Kennedy KF, et al. Endovascular versus surgical revascularization for chronic mesenteric ischemia: insights from the National Inpatient Sample database. *JACC Cardiovasc Interv*. 2017;10:2440-2447.
8. Oderich GS, Erdoes LS, Lesar C, et al. Comparison of covered stents versus bare metal stents for treatment of chronic atherosclerotic mesenteric arterial disease. *J Vasc Surg*. 2013;58:1316-1323.
9. Alahdab F, Arwani R, Pasha AK, et al. A systematic review and meta-analysis of endovascular versus open surgical revascularization for chronic mesenteric ischemia. *J Vasc Surg*. 2018;67:1598-1605.
10. Menges A-L, Reutersberg B, Busch A, et al. Early and midterm outcomes of open and endovascular revascularization of chronic mesenteric ischemia. *World J Surg*. 2020;44:2804-2812.
11. Oderich GS, Bower TC, Sullivan TM, et al. Open versus endovascular revascularization for chronic mesenteric ischemia: risk-stratified outcomes. *J Vasc Surg*. 2009;49:1472-1479.e3.

22 Renal Denervation

STEFAN BERTO, KOLJA SIEVERT, ALOK SHARMA, PAMELA ILIOSKA,
MARKUS REINARTZ, DAGMARA HERING, JOHN OSBORN, AND HORST SIEVERT

INTRODUCTION, 385

ROLE OF THE KIDNEYS IN HYPERTENSION, 385

ANATOMY AND PHYSIOLOGY OF THE RENAL SYMPATHETIC NERVOUS SYSTEM, 386

Efferent Fibers, 386

Afferent Fibers, 388

ANIMAL AND HUMAN DATA SUPPORTING A LINK BETWEEN THE RENAL SYMPATHETIC NERVOUS SYSTEM AND HYPERTENSION, 388

PERCUTANEOUS RENAL SYMPATHETIC DENERVATION: EARLY TRIALS USING A SINGLE ELECTRODE RADIOFREQUENCY CATHETER, 389

LIMITATIONS OF EARLY TRIALS, 390

SYMPPLICITY HTN-3, 390

NEWER GENERATION DEVICES, 391

SPYRAL Catheter, 391

Recor Medical Paradise System, 392

Peregrine Device, 393

PRACTICAL ASPECTS: PATIENT SELECTION AND PERFORMANCE OF THE PROCEDURE, 394

Case Selection, 394

Patient Selection, 394

PROCEDURE, 397

Antiplatelet Therapy and Anticoagulation, 397

Access, 397

Angiography, 397

CURRENTLY COMMERCIALY AVAILABLE CATHETERS, 398

SPYRAL Catheter System, 398

The Recor Medical Paradise System, 399

THE PEREGRINE SYSTEM, 399

Sedation, Analgesia, and Other Necessary Medications, 399

Equipment, 399

EFFECT OF RENAL DENERVATION ON CONDITIONS OF SYMPATHETIC OVERACTIVITY OTHER THAN HYPERTENSION, 400

Diabetes Mellitus and the Metabolic Syndrome, 400

Renal Insufficiency, 400

Atrial Fibrillation, 400

Ventricular Arrhythmias, 401

Obstructive Sleep Apnea, 401

SYMPATHETIC NERVE ACTIVITY MAPPING AND TAILORED ABLATION, 402

CONCLUSIONS, 402

INTRODUCTION

Hypertension is a leading cause of death worldwide with 13% of all deaths attributed to it in 2004 (World Health Organization, 2009). A prevalence of 29% (1.56 billion) has been predicted for 2025.¹ In the United States, approximately 65 million individuals have hypertension.² It is associated with cardiovascular and cerebrovascular morbidity and mortality with a direct relationship of blood pressure and event risk.³ Antihypertensive therapy has been shown to reduce strokes, heart attacks, and cardiovascular deaths.^{4,5} However, some patients' blood pressures remain in a suboptimal range despite multidrug antihypertensive therapy. If the blood pressure remains below target despite three or more antihypertensive medications of different classes, one of which optimally should be a diuretic, or requires four or more antihypertensive medications for adequate control, it is generally considered to be "resistant."⁶ The reported prevalence of resistant hypertension varies widely depending on definitions used and populations studied. In some non-population-based tertiary referral studies⁷ and clinical trials,⁸⁻¹⁰ the prevalence ranges between 12% and 34%. In population-based studies, the reported prevalence is lower. For example, in the National Health and Nutrition Examination Surveys (NHANES), it was 9%,¹¹ and in a population study from northern California and Colorado, it was 2%.¹² Risk factors for developing resistant hypertension include male gender, age, diabetes, obesity, chronic kidney disease (CKD), and Framingham 10-year

coronary risk greater than 20%.^{12,13} Importantly, patients with resistant hypertension have a higher risk for cardiovascular events.¹² The sympathetic nervous system plays a substantial role in development and maintenance of resistant hypertension and has recently been the target of catheter-based intervention. In this context, the physiology of the renal sympathetic nervous system, the role in hypertension, and the effects and techniques of interrupting the renal sympathetic nervous system are discussed.

ROLE OF THE KIDNEYS IN HYPERTENSION

Before reviewing specifics of the renal sympathetic nervous system in blood pressure regulation, an important concept should be mentioned first: the kidneys have a dominant role in blood pressure control.¹⁴ This has been shown by kidney cross transplantation. When kidneys from hypertensive rats are removed and implanted into normotensive rats and vice versa, normotensive rats become hypertensive and hypertensive rats normotensive.¹⁵ It is therefore the kidney and not the host that primarily determines blood pressure. The kidneys' ability to regulate blood pressure can take place (regardless of external influences) by the principle of pressure natriuresis, which is the ability to conserve or excrete sodium and water to an extent that maintains blood pressure at an *intrinsic goal unique to the kidney*. In support of this concept, when kidneys are isolated from external influences by

denervation, bilateral adrenalectomy, and continuous infusion of high doses of catecholamines and glucocorticoids, cross clamping the aorta (thereby increasing perfusion pressure of the kidneys) causes pronounced natriuresis and diuresis.^{16,17} Hence, the kidneys largely determine blood pressure by maintaining an intrinsic blood pressure goal by pressure natriuresis. Although this can be achieved in the absence of external influences, external signals can change the intrinsic blood pressure goal. One such signal comes from the renal sympathetic nervous system.

ANATOMY AND PHYSIOLOGY OF THE RENAL SYMPATHETIC NERVOUS SYSTEM

Every component of the kidney is supplied by *efferent* sympathetic nerve fibers.¹⁸⁻²¹ Equally important, the kidneys send signals to the central nervous system (CNS) via *afferent* sympathetic fibers.

Efferent Fibers (Figure 22.1)

Signals from the CNS (amygdala, ventrolateral nucleus of the hypothalamus, cortex, pons) and chemo- and baroreceptors are integrated in the medulla oblongata (solitary tract nucleus and rostral ventral medulla oblongata) from where sympathetic nerve fibers course within the spinal cord to the intermediolateral nucleus (T10–L2).²² In the intermediolateral nucleus, signals are relayed to presynaptic fibers that exit the spinal cord and terminate at postsynaptic fibers in the celiac, superior, and inferior mesenteric

ganglion. Postsynaptic fibers (located predominantly within the adventitia of the renal arteries) supply the tubulointerstitial cells, granular cells of the juxtaglomerular apparatus, and arteriolar smooth muscle cells. Norepinephrine and neuropeptide Y are released (Figure 22.2). Norepinephrine binds to both α -1b receptors and β -receptors (located in the apical membrane of the tubulointerstitial cells^{23,24}), causing stimulation²⁵ and inhibition²⁶ of the sodium/potassium ATPase, respectively, with an overall neutral effect. However, neuropeptide Y enhances the stimulatory effect of norepinephrine.²⁶ The net effect is a stimulation of the sodium/potassium ATPase, causing sodium and water retention and a blood pressure increase. At the granular cells of the juxtaglomerular apparatus, norepinephrine binds to β -1 receptors causing G protein-coupled activation of adenylyl cyclase, generating cyclic AMP that stimulates renin release (Figure 22.3).²⁷ Renin causes activation of the renin-angiotensin system, generating angiotensin II and aldosterone, causing vasoconstriction and sodium and water retention, respectively, with subsequent blood pressure increase.²⁸ Hormones of the angiotensin-aldosterone system also cause vascular remodeling^{28,29} and changes in cardiac architecture such as left ventricular hypertrophy and fibrosis.³⁰ At arteriolar smooth muscle cells, norepinephrine binds to α -1a receptors and (via G protein-coupled mechanism) activates phospholipase C, releasing inositol trisphosphate and diacylglycerol (Figure 22.4).³¹ Inositol trisphosphate stimulates calcium release from the sarcoplasmic reticulum that binds to the contractile apparatus triggering smooth muscle contraction and vasoconstriction.³²

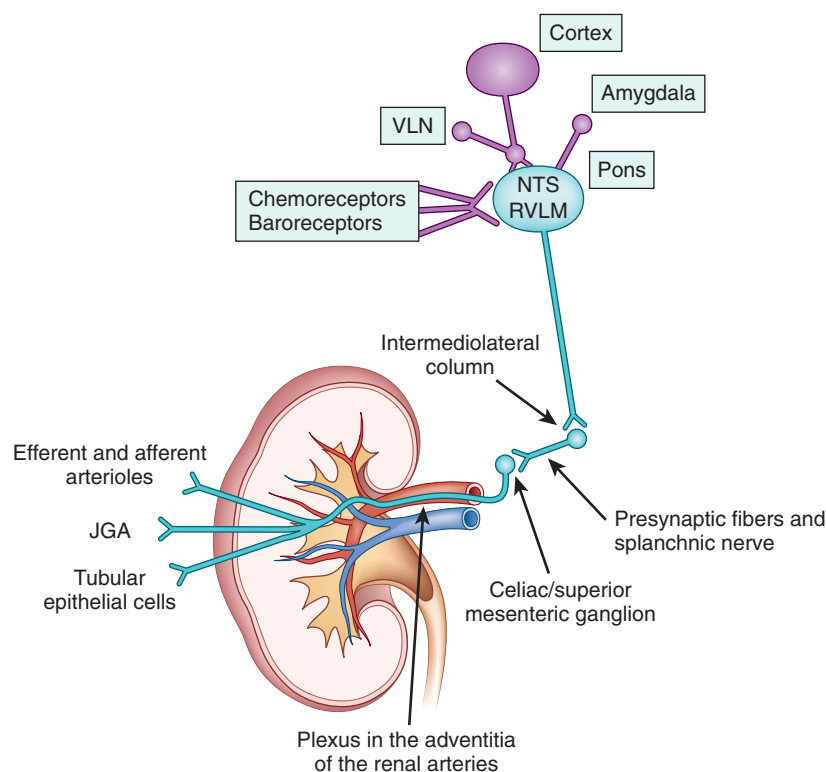


FIGURE 22.1 The anatomy of the efferent renal sympathetic nervous system (for description, please see text). JGA, Juxtaglomerular apparatus; NTS, solitary tract nucleus; RVLM, rostral ventrolateral medulla; VLN, ventrolateral nucleus of the hypothalamus.

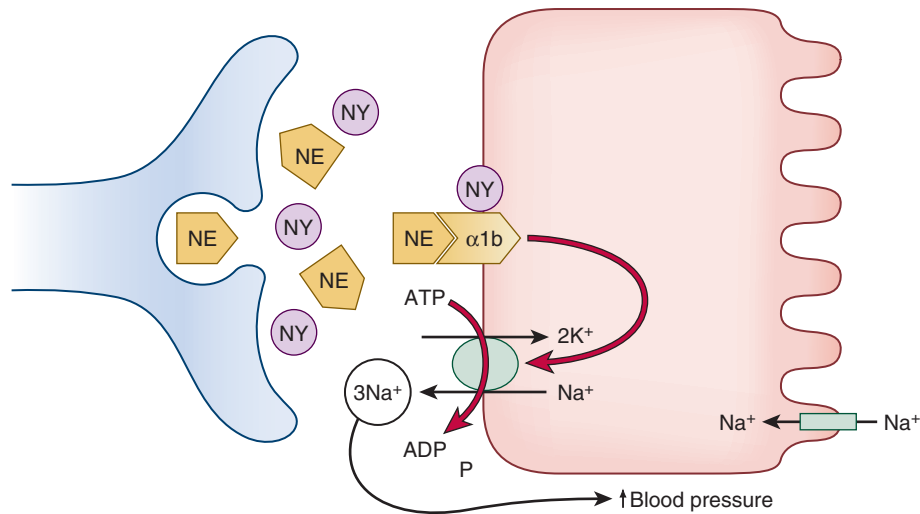


FIGURE 22.2 The efferent sympathetic fiber endings at the adluminal membrane of the tubuloe epithelial cells on a cellular or molecular level (please refer to text for description). Not illustrated: the inhibitory effect of norepinephrine on the beta-receptor. *ADP*, Adenosine diphosphate; *ATP*, adenosine triphosphate; K^+ , potassium; Na^+ , sodium; *NE*, norepinephrine; *NY*, neuropeptide Y; *P*, phosphate.

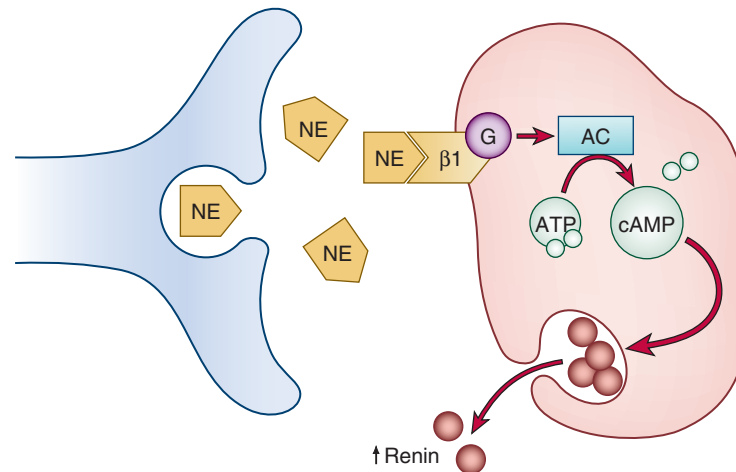


FIGURE 22.3 The efferent sympathetic nerve fiber endings at the juxtaglomerular apparatus on a cellular or molecular level (please refer to text for description). *AC*, Adenyl cyclase; *ATP*, adenosine triphosphate; *cAMP*, cyclic adenosine monophosphate; *G*, G protein; *NE*, norepinephrine.

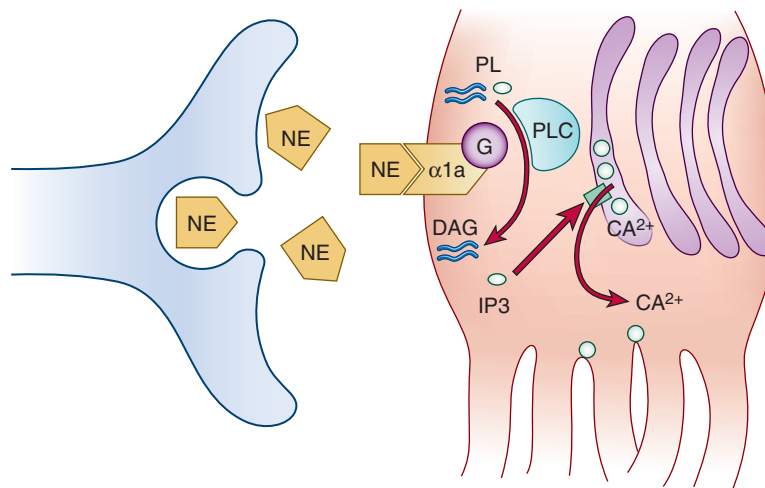


FIGURE 22.4 Illustration of the efferent sympathetic nerve fiber ending at the renal arterioles on a cellular or molecular level (please see text for description). Ca^{2+} , Calcium; *DAG*, diacylglycerol; *G*, G protein; *IP₃*, inositol trisphosphate; *NE*, norepinephrine; *PL*, phospholipid; *PLC*, phospholipase C.



Afferent Fibers

Renal afferent nerve fiber endings are located predominantly in the renal pelvis.³³ It is important to note that there is an abundance of sensory fibers in all layers of the renal pelvis, including the epithelial, subepithelial, and smooth muscle layers.³⁴⁻³⁶ In addition, the distance between the sensory fibers and the inner surface of the renal pelvis is typically very short (~1 mm). However, some fibers are also adjacent to the arterioles and veins within the kidney parenchyma as well as in proximity to the glomeruli.^{34,37,38} Mechano- and chemoreceptors stimulate the renal afferent nervous system.³⁹ Mechanoreceptors provide feedback on hydrostatic pressure within the renal pelvis, arteries, and veins. Chemoreceptors are a gauge for the renal interstitial milieu and are activated by mediators released during renal parenchymal ischemia. Signals are relayed from the kidneys via afferent sympathetic fibers with nuclei located in the dorsal root ganglia to the ipsilateral posterior gray column (lamina I-III). The neurotransmitters are substance P and calcitonin gene-related peptide. Signals are then further transmitted from the spinal cord to CNS autonomic centers (paraventricular nucleus of the hypothalamus and solitary tract nucleus in the brainstem) and to the contralateral kidney.^{40,41} Autonomic center stimulation, in turn, increases the overall sympathetic tone, causing vasoconstriction, fluid retention, and, consequently, blood pressure increase. The concept that stimulation of afferent sensory nerves causes an increase in sympathetic tone is supported by animal models (rats) that undergo intrarenal administration of bradykinin, a substance known to activate sensory nerves, causing blood pressure and heart rate increases.⁴² Stimulation of the contralateral kidney alters the sodium and water balance (renorenal reflex). The impact of renal afferent sympathetic nervous stimulation on blood pressure has been shown in animal studies that target activation or inhibition of afferent fibers. Renal injury in rats by toxin injection or ischemia results in activation of the afferent sympathetic fibers, causing an increase in overall sympathetic nervous system activity and blood pressure that can be attenuated or prevented by prior dorsal rhizotomy (transection of the dorsal roots [the equivalent to interruption of the afferent sympathetic pathway]).⁴³⁻⁴⁵ Likewise, a blood pressure reduction has been shown in renal insufficiency rat models after dorsal rhizotomy. In this model, the hypertensive response after near-total nephrectomy is less pronounced if these animals have first undergone dorsal (T10-L2) rhizotomy.⁴⁶

More recent data support the concept that inflammation may cause activation of sensory nerves, and vice versa, activation of efferent renal sympathetic fibers may cause inflammation. In support of this concept are experiments in which animals are exposed to an infection (e.g., injection of colonic bacteria). In those who underwent prior renal denervation, the inflammatory response was attenuated.⁴⁷ In patients with nephritis, renal denervation caused a reduction in proteinuria.⁴⁸ In addition, improvement in glomerulonephritis, and inhibition of the inflammatory and fibrotic response after ureteral obstruction has been demonstrated with prior renal denervation.^{49,50} Finally in a DOCA (11-Deoxycorticosterone

acetate)-salt rat model, it has been shown that renal denervation attenuates the proinflammatory response.⁵¹

ANIMAL AND HUMAN DATA SUPPORTING A LINK BETWEEN THE RENAL SYMPATHETIC NERVOUS SYSTEM AND HYPERTENSION

Several pivotal animal experiments, in addition to those previously described, warrant mention. Direct stimulation of the splanchnic nerve in a dog model causes a blood pressure increase,⁵² whereas interruption of the renal sympathetic fibers (by removal and reimplantation of the kidneys) causes diuresis and blood pressure reduction. Similarly, splanchnic nerve transection causes natriuresis and diuresis.⁵³ An increase in blood pressure seen in the Goldblatt model of a single kidney supplied by a stenotic artery or in the Goldblatt two kidneys, one-clip model (only one of the renal arteries has a stenosis in this model) can be attenuated by denervation of the clipped renal artery.⁴⁴ Hypertension in a rat model caused by renal injury, for example, by intrarenal phenol injection, can be attenuated by renal sympathetic denervation.⁴³ Comparison of genetically spontaneous hypertensive rats with genetically normotensive rats identified increased renal sympathetic nerve activity in the hypertensive rats.⁵⁴ Renal denervation in spontaneous hypertensive rats was shown to delay the onset of hypertension and to mitigate the hypertensive response.⁵⁵ It is noteworthy that hypertension returned to spontaneously hypertensive because of reinnervation of renal sympathetic nerves but was again attenuated by repeat denervation.⁵⁶ Renal denervation in other animal hypertensive models, including other rats, dogs, pigs, and rabbits, has also been shown to prevent or delay the development of hypertension and diminish the severity of hypertension.⁵⁷

In humans, the sympathetic nervous system has been shown to play an important role in the pathogenesis and maintenance of hypertension. Increased plasma catecholamine levels have been shown in borderline hypertension⁵⁸ and in young patients with hypertension.⁵⁹ However, the plasma catecholamine concentrations are not universally elevated. Particularly in older patients with hypertension, levels similar to those in normotensive individuals have been reported.⁶⁰ Plasma catecholamine concentrations not only depend on its release at the nerve terminals but also on metabolism and reuptake. In addition, differences in sympathetic nerve activity between end organs have been demonstrated^{61,62}; therefore, it may not consistently reflect overall and regional sympathetic nervous system activity. Instead, muscle sympathetic nervous system activity and norepinephrine spillover measurements are more reliable indicators of overall and regional sympathetic tone. In this context, compared with normotensive individuals, higher muscle sympathetic nerve activity and reduced norepinephrine reuptake have been described in patients with hypertension.^{60,62-64} Increased sympathetic nerve activity has also been identified in individuals with secondary hypertension related to renal artery stenosis, obesity, and obstructive sleep apnea (OSA).⁶⁵⁻⁶⁷

The consequences of interrupting the renal sympathetic nervous system on blood pressure have also been demonstrated in humans. The increased sympathetic tone in patients with CKD requiring dialysis normalizes after bilateral nephrectomy.⁶⁸ The increased sympathetic activity persists after kidney transplant if the native kidneys remain.⁶⁹ Blood pressure reductions after nephrectomy in patients with kidney disease, including those with unilateral disease and single nephrectomy (e.g., for pyelonephritis or congenital hypoplasia)⁷⁰⁻⁷² and in patients with bilateral disease and bilateral nephrectomy, have been reported.^{73,74} Although the improvements in blood pressure control could be explained by elimination of sympathetic signals to and from the diseased kidneys, it is also possible that explantation of the diseased kidneys causes the blood pressure improvement by a reduction in renin-angiotensin-aldosterone system activity that is typically increased in patients with CKD whose kidneys remain in place. However, the renal sympathetic nervous system appears to have a greater impact. For example, patients with CKD generally experience a greater blood pressure reduction with central sympatholytic therapy (e.g., clonidine) than with blockade of the renin-angiotensin system.⁷⁵ The mechanism for increased renal sympathetic activity is unclear but could be related to renal ischemia because sympathetic nervous system activity decreases after angioplasty in patients with renal artery stenosis.⁷⁶ Blood pressure has also been shown to improve after unilateral nephrectomy in patients with renal artery stenosis.⁷⁷

Surgical sympathectomy provides further insight into the role of the renal sympathetic nervous system in hypertension control. It was used to treat severe hypertension until the 1970s and involved resection of distal thoracic and proximal lumbar sympathetic ganglia and bilateral splanchnic nerve transection.^{78,79} The surgery was accompanied by dramatic blood pressure⁷⁹⁻⁸² and mortality^{79,83-85} reductions compared with control groups. Furthermore, improvements in cardiac size,^{86,87} precordial pain,⁸⁸ renal function,⁸⁶⁻⁸⁸ cerebrovascular events,⁸⁸ and headaches⁸⁸ were reported. However, these studies were uncontrolled, nonrandomized comparisons subject to several limitations related to the placebo effect, the Hawthorne effect, selection bias, and patient and operator bias. Operative morbidity and mortality together with the advent of novel antihypertensive agents led to the discontinuation of surgical sympathectomy for the treatment of hypertension in the 1970s. Nonetheless, the results further support the importance of the renal sympathetic nervous system in the pathogenesis of hypertension and potential benefits after sympathectomy.

PERCUTANEOUS RENAL SYMPATHETIC DENERVATION: EARLY TRIALS USING A SINGLE ELECTRODE RADIOFREQUENCY CATHETER

The aforementioned physiological and clinical observations underlining the importance of the renal sympathetic nervous system in blood pressure control and the convenient location of the sympathetic nerve fibers (predominantly in the renal artery adventitia and perivascular



FIGURE 22.5 Image illustrating the Symplicity Flex Renal Denervation System (Reproduced with permission of Medtronic, Inc.). The generator is shown and the Symplicity catheter.

space) led to the concept and evaluation of catheter-based renal sympathetic denervation by radiofrequency application. The efficacy and safety were first assessed in pigs. Renal denervation using the Symplicity Flex Renal Denervation System (Medtronic) (Figure 22.5) was accompanied by histologic evidence of neuronal injury in the perivascular space of the renal artery as well as a reduction in sympathetic axons in the renal cortex (by tyrosine hydroxylase staining) and a 90% reduction in renal norepinephrine concentration (unpublished report by Medtronic). Optical coherence tomography examination of the renal artery after renal denervation in a pig demonstrated endothelial denudation and transmural tissue coagulation followed by tissue fibrosis and reendothelialization and renal nerve necrosis 10 days after ablation.⁸⁹ Six months after ablation, histology demonstrated necrotic nerve fibers and fibrosis involving 10% to 25% of the media and adventitia without stenosis.⁹⁰

In the Symplicity-1 trial, 45 patients with severe resistant hypertension underwent radiofrequency renal sympathetic denervation with a single electrode catheter.⁹¹ A significant 27/17-mm Hg 1-year office blood pressure reduction was observed. An increase in antihypertensive therapy occurred in 4 patients; however, a significant and pronounced blood pressure reduction remained after excluding these patients from analysis. In addition, blood pressure medications were reduced in 9 patients because of improved blood pressure control. Thirteen percent of patients were considered nonresponders (defined as systolic blood pressure [SBP] reduction of <10 mm Hg). Ambulatory blood pressure reductions were less pronounced (11 mm Hg systolic) than office blood pressures, a common theme in all subsequent studies examining renal denervation.

Renal and total-body norepinephrine spillover decreased after renal denervation ($n = 10$), supporting the notion that renal denervation reduces renal and overall sympathetic nervous system activity. A reduction in overall sympathetic tone assessed by muscle sympathetic nerve activity has been demonstrated in one patient from the Symplicity HTN-1 trial⁹² and subsequently in a separate study.⁹³ One guide catheter-induced renal artery dissection requiring stenting and one femoral artery pseudoaneurysm were reported.



In a registry including Symplicity HTN-1 patients and others, office blood pressure reductions were durable at 33/14 mm Hg at 24 months⁹⁴ and 32/14 mm Hg at 36 months ($n = 87$) regardless of age, diabetic status, or baseline renal function.⁹⁵ Furthermore, the responder rate increased over time from 70% at 1 month to 93% at 36 months.⁹⁵ One de novo renal artery stenosis possibly related to renal denervation requiring stenting, one renal artery stenosis at a site remote from the treatment site (with some degree of preexistent stenosis) requiring stenting, and two hemodynamically insignificant mild renal artery stenoses were reported throughout the 36-month follow-up.

In Symplicity HTN-2 ($n = 106$), patients with severe resistant hypertension were randomized to renal sympathetic denervation with a single-electrode radiofrequency catheter (in addition to conventional medical therapy) or conventional medical therapy alone.⁹⁶ There was a significant 32/12-mm Hg office blood pressure reduction in the denervation group versus none in the control group at 6 months with a responder rate of 84% (vs 35% in the control group). The ambulatory (11/7 mm Hg) was again less pronounced than the office blood pressure reduction after renal denervation, but it remained significant (versus no change in the control group). There were no major adverse events. No changes in renal function or urine albumin to creatinine ratios were seen in either group. Forty-six patients from the control group crossed over to renal denervation and experienced a significant 24/8-mm Hg blood pressure reduction 6 months after crossover.⁹⁷ In addition, a lasting 33/14-mm Hg reduction in office blood pressure has been demonstrated in the 40 patients of the initial group who underwent 36-month follow-up.⁹⁷

Renal denervation has more recently been studied in a small number ($n = 20$) of patients with milder forms of resistant hypertension (office SBP, 140–160 mm Hg) with significant 13/5-mm Hg office and 11/4-mm Hg ambulatory blood pressure reductions at 6 months.⁹⁸ Similar findings were reported subsequently in 54 patients with mild resistant hypertension with 13/7- and 14/7-mm Hg office and ambulatory blood pressure reductions at 6 months, respectively.⁹⁹ Therefore, it appears that hypertension severity predicts the magnitude of response.

LIMITATIONS OF EARLY TRIALS

All limitations that accompany unblinded studies without a control group, including selection and observer bias, placebo effect, and Hawthorne effect, apply to Symplicity HTN-1, and the same limitations, with the exception of selection bias, apply to Symplicity HTN-2. In addition, given inclusion of patients into the study based on office SBP and comparison of follow-up blood pressure to the blood pressure used for inclusion, regression to the mean may lead to overestimation of the treatment effect. Although it does not eliminate regression to the mean, comparison of ambulatory blood pressures before and after treatment attenuates (but does not eliminate) the consequences of this statistical phenomenon. It is therefore not surprising that ambulatory blood pressure effects are invariably

lower than office blood pressure effects unless measures are taken to prevent regression to the mean.

Any injury to the renal artery as it occurs with radiofrequency or ultrasound energy application may, in addition to the intraprocedural risk of renal artery dissection or thrombus formation with or without embolization, lead to renal artery stenosis. In this context, pulmonary vein stenosis has been reported after radiofrequency application for the purpose of pulmonary vein isolation in patients with atrial fibrillation.¹⁰⁰ However, the radiofrequency energy used for renal denervation (e.g., 8 W with the [single-electrode] Symplicity Renal Denervation System) is lower than for pulmonary vein isolation (≤ 30 W). In studies with imaging follow-up, renal artery stenosis has been a rare event. For example, at 36-month follow-up of Symplicity HTN-1 and registry patients, only 1 of 153 patients was found to have a renal artery stenosis potentially related to renal denervation requiring stenting.⁹⁵ Nevertheless, renal artery stenoses have been reported not only with radiofrequency^{101,102} but also with ultrasound energy application.¹⁰³ It is noteworthy that imaging follow-up in many studies is limited, and the exact incidence of renal artery stenoses at long-term follow-up remains to be determined.

Renal denervation has not led to meaningful blood pressure responses in approximately 15% of patients for unclear reasons. Possibilities include incomplete denervation caused by technical limitations, procedural shortcomings, or the presence of hypertension not driven by sympathetic overactivity. In this context, it would be desirable to measure renal or overall sympathetic nerve activity routinely before, during, and after renal denervation; however, this is cumbersome and not without risks (norepinephrine spillover measurements require invasive measurements). Moreover, it is also not clear whether such measurements would help predict clinical success. Discrepant regional sympathetic activity may further complicate matters. For example, in some patients with hypertension, renal norepinephrine spillover is normal, but muscle sympathetic nerve activity is increased.⁶²

The possibility of renal sympathetic reinnervation has been raised because it occurs in some animal models.⁵⁶ Moreover, sympathetic cardiac reinnervation has been described in humans after heart transplantation.¹⁰⁴ In this context, histologic examination of transplanted kidneys suggest reinnervation,¹⁰⁵ but it does not appear to be of functional relevance.¹⁰⁶ The durability of blood pressure reductions in Symplicity HTN-1 and 2 (described earlier) does not suggest relevant sympathetic reinnervation, at least up to 36 months.

SYMPLECTICITY HTN-3

The potential shortcomings of Symplicity HTN-1 and -2 mentioned earlier and of a number of other uncontrolled studies demonstrating a blood pressure reduction have led to the performance of the Symplicity HTN-3.¹⁰⁷ In this trial, maximum efforts were made to minimize the possibility that a blood pressure difference between the treatment and control group might be driven by placebo and Hawthorne effect by randomly assigning patients with

resistant hypertension to renal denervation or a sham procedure (renal angiography without denervation) in a 2:1 fashion with blinding of investigators and patients at follow-up. The design also eliminated a potential operator and patient bias. A total of 535 patients were enrolled. Renal denervation with the Symplicity Flex Renal Denervation System was performed in patients assigned to renal denervation (in 364 patients) and renal artery angiography in the control group. Endpoints were safety (composite of death from any cause, end-stage renal disease, embolic event resulting in end-organ damage, vascular complications, hypertensive crisis within 30 days, or renal artery stenosis within 6 months) and efficacy (change in office SBP at 6 months with a superiority margin of 5 mm Hg). The study demonstrated an excellent safety profile. There was no significant difference in the composite safety endpoint at 6 months (4% in the renal denervation group vs 5.8% in the sham group). There was also no significant difference in the number of major adverse events (1.4% in the denervation group vs 0.6% in the sham group). However, although the office SBP decreased in both groups (by 14 mm Hg in the denervation group vs 11.7 in the sham group), there was no significant difference between the groups (2.39 mm Hg). Likewise, there was no significant difference in ambulatory blood pressure reduction between the groups (reduction of 6.8 mm Hg in the denervation group vs 4.8 mm Hg in the sham group). The reason for the discrepant findings between the first two Symplicity trials and several other studies demonstrating a favorable blood pressure response and Symplicity HTN-3 remains unclear. It is possible that effects of previous trials were artificial and driven by the limitations described earlier, particularly regression to the mean, also referred to as “big day bias” (by which the blood pressure that was used to enter the trial was also used as the baseline), placebo or Hawthorne effect, and observer bias. However, several aspects deserve consideration.

First, sound physiological evidence supports a reduction in renal and overall sympathetic nervous system activity after renal denervation both from animal and human experience described in detail previously. This suggests the possibility of technical limitations in the trial. It is, for example, conceivable that the procedural technique did not lead to the desired interruption of the renal sympathetic nervous fibers. In this context, it has been pointed out that the mean number of ablations (3.9 per artery) was smaller than is common practice. However, the number of ablations was no different in Symplicity HTN-1 (4 per artery), and it has yet to be shown that the number of ablations corresponds to efficacy. Furthermore, operator experience was limited as reflected by the number of procedures per operator. Only one denervation was performed by 31% of operators, and all procedures (364) were performed by 111 operators (average number of procedures, 3.3). It is therefore possible that limited experience may have affected the efficacy. Yet there was no difference in efficacy between operators who performed five or more and those who performed five or fewer procedures. Furthermore, there was no difference in efficacy when results after first were compared with later denervations.

Second, patient selection may have influenced the results. It is possible that patient characteristics differed between patients enrolled in Symplicity HTN-3 and prior studies. To this effect, subgroup analyses have been performed and demonstrated a more pronounced office blood pressure reduction with a significant difference compared with the sham group in patients who were not of African American descent, patients younger than 65 years, and those with a glomerular filtration rate (GFR) of 60 mL/min/173 m² or greater. In this context, in the population in which renal denervation was studied and taking a smaller treatment effect than predicted into account, Symplicity HTN-3 may have been underpowered to demonstrate a significant difference in blood pressure reductions between the treatment and control groups. It should be noted, however, that the ambulatory blood pressure monitoring did not confirm a significant effect in the above subgroups.

However, it should be mentioned that the final follow-up of SYMPPLICITY HTN-3 did suggest a significant blood pressure reduction from renal denervation even with the older generation (Symplicity Flex) catheter that only became more apparent with longer-term follow-up and potential attenuation of any placebo or Hawthorne effects.¹⁰⁸ In fact, at 36 months, the change in office systolic blood pressure was -26 mm Hg in the renal denervation group and 6 mmHg in the sham control group (adjusted treatment difference 22 mmHg, $p < 0.0001$). The 24 hour ambulatory systolic blood pressure reduction at 26 months was -16 mmHg in the denervation group versus -0.3 mmHg in the sham control group ($p < 0.0001$). In addition, blood pressures in the renal denervation group were in the therapeutic range significantly longer than in the sham group (18% versus 9% $p < 0.0001$). There was no evidence of late procedure related adverse events. There was no difference in the composite safety endpoint at 48 months (including all-cause death, new onset end-stage renal disease, embolic events, vascular complications, renal artery reintervention or hypertensive crises). These findings suggest that longer term follow-up may be very important when examining the potential benefits of renal denervation.

NEWER GENERATION DEVICES

Since the publication of Symplicity HTN-3, several important trials have been performed with devices that have addressed some of the potential shortcomings of the single-electrode Symplicity catheter, and more are currently ongoing.

SPYRAL Catheter

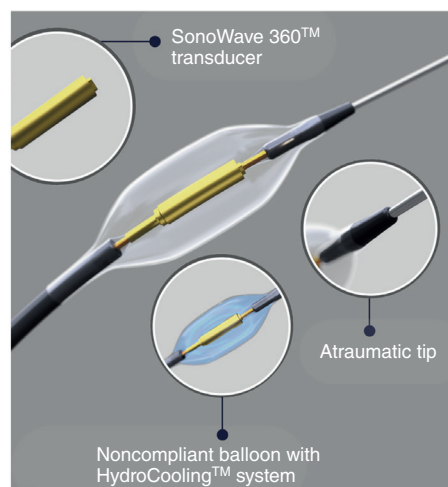
In the Global Clinical Study of Renal Denervation With the Symplicity Spyral™ Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medication (SPYRAL HTN-OFF MED) trial ($n = 331$) using the multi-electrode SPYRAL catheter (Medtronic; Figure 22.6), patients taking no antihypertensive medications with office SBP of 150 to 180 mm Hg (and diastolic blood pressure [DBP] of ≥ 90 mm Hg) were randomly assigned to renal denervation or a sham



FIGURE 22-6 This figure illustrates the SPYRAL catheter and generator (Reproduced with permission of Medtronic, Inc.)



FIGURE 22.7 The Recor Medical Paradise System (ReCor Medical).



procedure.^{109,110} All caregivers performing clinical follow-up were blinded to the treatment. The primary endpoint was the change in ambulatory blood pressure at 3 months. In the treatment group, the ambulatory SBP reduction was 3.9 mm Hg greater compared with the sham group ($P < .05$). In addition, in the treatment group, the office SBP was 6.5 mm Hg lower than in the sham group. There was, furthermore, a significant difference in ambulatory DBP (3.1 mm Hg) in favor of denervation. Importantly, at 3 months, there were no procedure- or device-related safety events. Important aspects are the mean patient age of 52 years and the requirement of combined hypertension for entry into the trial.

In SPYRAL HTN-ON MED, patients with uncontrolled hypertension (taking one to three medications) were randomized to denervation or sham (renal angiography). Patients and all subsequent caregivers were blinded to the treatment. After 80 patients were enrolled, a preliminary analysis demonstrated a significantly more pronounced ambulatory SBP (by 7.4 mm Hg) and DBP (by 4.1 mm Hg) reduction after denervation compared with sham. The mean age in this patient population was 54 years.¹¹¹ The efficacy and safety were further assessed at 3 years and demonstrated a lasting and more pronounced effect in favor of the denervation group (the 24-hour ambulatory

SBP and DBP were 10 and 11 mm Hg lower, respectively).¹¹² It is important to mention that there was no significant difference in the medication burden between the groups at follow-up (2.13 medications in the renal denervation group vs 2.6 medications in the sham group).

ReCor Medical Paradise System

The Recor Medical Paradise system (ReCor Medical; [Figure 22.7](#)) system was first available in 2012 for treatment of patients with resistant hypertension. The first-in-human single-arm study ($n = 11$) demonstrated a significant reduction in office and ambulatory blood pressures in patients with resistant hypertension.¹¹³ Given a concern for renal artery stenosis related to the focal circumferential energy emission, the recommended flow rate of the cooling solution was increased. Efficacy and safety were subsequently studied in the REnAL denervation by ultraSound Transcatheter Emission (REALISE) ($n = 20$) and TrAnsCatHeter Intravascular Ultrasound Energy deliV-ery for rEnAl Denervation (ACHIEVE) ($n = 96$) studies.^{114,115} The latter demonstrated a 7.5-mm Hg reduction in ambulatory SBP pressure at 12-month follow-up in patients with resistant hypertension. No renal artery stenoses occurred.

More recently, results of the Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE) trial have been published. This was a randomized, placebo- and sham-controlled trial with two study arms. In the first, the SOLO arm ($n = 146$), patients with moderate hypertension (taking zero to two medications) discontinued their antihypertensive medications and underwent renal denervation or a sham procedure.¹¹⁶ Renal denervation was accompanied by a significant 4.1-mm Hg reduction (compared with sham) of ambulatory SBP at 2-month follow-up. A favorable effect was maintained at 6 months *only when adjusted for the number of antihypertensive medications*.¹¹⁷ Although there was no significant difference in ambulatory blood pressure at 12 months, patients were taking significantly less antihypertensive medications in the treatment group.¹¹⁸ Furthermore, in patients who were initially assigned to the sham group and ultimately crossed over to denervation, there was a 10.8-mm Hg reduction in ambulatory SBP 6 months after denervation.¹¹⁹ In the TRIO arm ($n = 136$), in patients with resistant hypertension, the antihypertensive regimen was changed to a single daily pill containing three antihypertensive agents (calcium channel blocker, angiotensin receptor blocker, and thiazide diuretic). In addition, patients were randomly assigned to denervation or sham. In patients who underwent renal denervation, at 2 months, there was a significant reduction in daytime ambulatory blood pressure by 4.5 mm Hg. In addition, there was a significant reduction in 24-hour ambulatory SBP favoring denervation (-4.2 mm Hg; $P = .016$), but there was no significant difference in DBP. After 2 months, antihypertensive medications were increased if blood pressure control was inadequate (home blood pressure measurement $>135/85$ mm Hg) with addition of spironolactone, bisoprolol, and a centrally acting alpha-2 receptor agonist and an alpha-1 receptor blocker. At 6 months, the number of added antihypertensive medications was higher (1.1) in the sham group compared with patients who underwent renal denervation (0.7; $P = .045$). At 6-month follow-up, there was no significant difference in ambulatory

blood pressures between the groups (abstract presented at Transcatheter Therapeutics [TCT] in Orlando 2021).

Results of another randomized trial (Renal Denervation on Quality of 24-hr BP Control by Ultrasound In Resistant Hypertension [REQUIRE])¹¹⁹ enrolling 143 patients with resistant hypertension in an Asian population have not been published or presented yet. Finally, the RADIANCE II pivotal trial is enrolling patients with mild to moderate hypertension, and assignment will be random in a 2:1 fashion to device therapy versus sham.¹¹⁹ Enrollment has been completed, and results have not yet been presented.

In the Randomized Comparison of Ultrasound Versus Radiofrequency Denervation in Patients With Therapy Resistant Hypertension (RADIOSOUND) trial patients with resistant hypertension were assigned to either denervation using the SPYRAL (radiofrequency) catheter in the main renal artery only; denervation using the SPYRAL catheter in the main renal artery, side branches, and accessory renal arteries; or renal denervation using the Recor Medical Paradise (ultrasound) system.¹²⁰ A total of 120 patients were enrolled. The trial demonstrated a more pronounced ambulatory daytime blood pressure reduction in patients who underwent ultrasound-mediated denervation compared with radiofrequency ablation (RFA) in the main renal arteries only. However, there was no significant difference between the ultrasound group and the group of patients who underwent RFA in the main renal arteries, side branches, and accessories when present.

Peregrine Device

There have been two randomized trials (A Pivotal, Multi-center, Blinded, Sham Procedure-Controlled Trial of Renal Denervation by the Peregrine System™ Kit, in Subjects With Hypertension [TARGET BP] ON and OFF med) ongoing designed in a similar fashion to SPYRAL HTN-ON and -OFF MED using the Peregrine device (alcohol-mediated ablation, Ablative; Figures 22.8 and 22.9). The results are expected in 2022 and 2023.

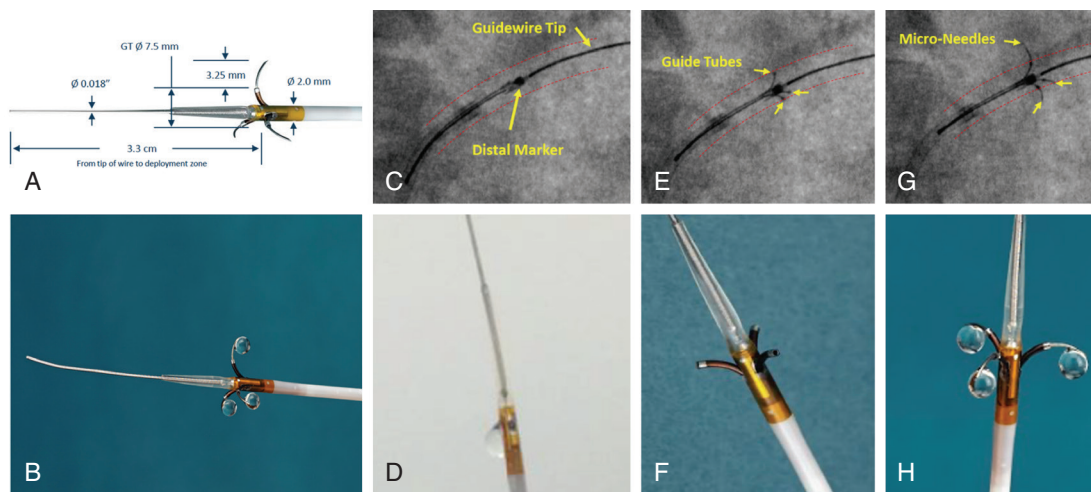


FIGURE 22.8 The Peregrine Catheter (Ablative Solutions, Wakefield, MA, USA). **A**, This figure illustrates the Peregrine Catheter tip with its specifications. Note, the distal tip is a flexible 0.018 inch wire that can be shaped similarly to a coronary wire. **B**, This figure illustrates the catheter tip during infusion of alcohol. **C**, This figure illustrates the fluoroscopic appearance of the Peregrine catheter tip with both guide tubes and microneedles retracted. **D**, This figure illustrates the Peregrine Catheter tip prior to insertion into the guide catheter. **E**, This figure illustrates the fluoroscopic appearance of the Peregrine Catheter tip with the guide tubes deployed. **F**, This figure illustrates the Peregrine Catheter tip with the guide tubes deployed outside the guide catheter. **G**, This figure illustrates the fluoroscopic appearance of the Peregrine Catheter tip with the guide tubes and microneedles deployed. **H**, This figure illustrates the Peregrine catheter tip with the guide tubes and microneedles deployed and alcohol infusion outside the guide catheter.



- A. Stabilization zone
B. Rotational control knob
C. Plunger
D. Handle lock clip
1. End cap on injection lumen
2. Guide tube flush port
3. Outter lumen flush port

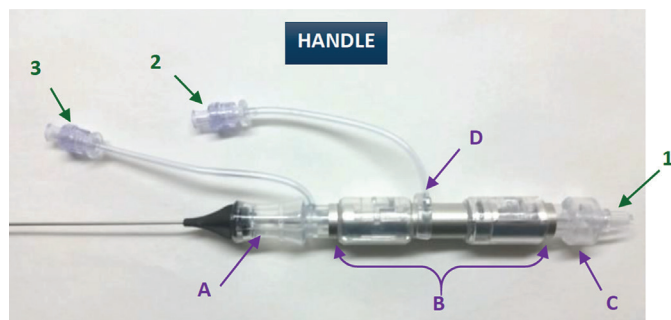


FIGURE 22.9 The Peregrine catheter handle (Ablative Solutions).

PRACTICAL ASPECTS: PATIENT SELECTION AND PERFORMANCE OF THE PROCEDURE

Case Selection

For the first few cases, for those who do not have prior experience with renal artery intervention, definition of the anatomy may be helpful for appropriate case selection. It may be prudent to select cases with no or only mild abdominal aortic tortuosity or atherosclerosis. Prior computed tomography angiography (CTA) or magnetic resonance angiography (MRA) outlines the abdominal aortic anatomy and illustrates potential challenges because of tortuosity or pronounced atherosclerosis. Some imaging software programs may allow determination of the optimal fluoroscopy angle to visualize the ostium and take-off of the renal artery. Of note, MRA using gadolinium is contraindicated in patients with a GFR below 30 mL/min. However, the use of special imaging techniques may allow adequate visualization of the aorta and renal arteries without the use of contrast.¹²¹⁻¹²⁴ Nevertheless, noninvasive imaging does not replace an abdominal aortography because all current methods—duplex ultrasonography, CTA, and MRA, may not adequately identify accessory renal arteries. Hence, generally, abdominal aortography should be part of most renal denervation procedures.

Patient Selection

Patient selection can be performed with a simple algorithm (Figure 22.10). The first question that must be answered is does the patient have severe resistant hypertension? In pivotal trials, *severe* resistant hypertension was defined as a blood pressure of 160 mm Hg or greater (or ≥ 150 mm Hg in the presence of diabetes mellitus).^{91,96} Milder forms of resistant hypertension appear to benefit from renal denervation, but the magnitude of blood pressure reduction is generally lower.^{98,99} Key elements of accurate office blood pressure measurement have been well described in the attached reference.¹²⁵ If it is measured accurately and the patient meets these criteria, the next step is to rule out white coat hypertension (normal blood pressures except when the patient is in a medical environment). This can be done with ambulatory blood

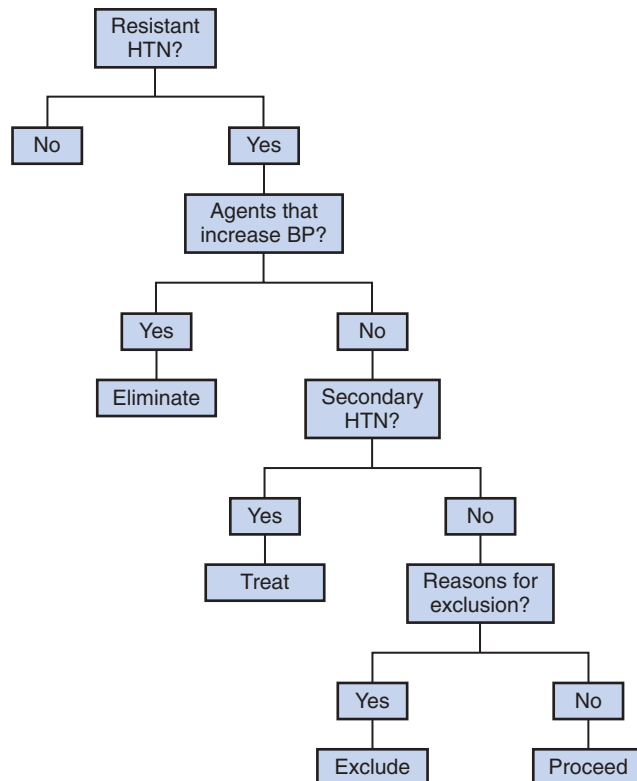


FIGURE 22.10 Patient selection for renal denervation. BP, Blood pressure; HTN, hypertension.

pressure measurement or, if unavailable, by periodic home blood pressure measurements, provided the patient's device is well calibrated. To eliminate the possibility of medical noncompliance, one might consider administration of all antihypertensive medications under the physician's or nurse's supervision before ambulatory blood pressure device hook up to assure at least compliance with morning medications. If there are serious doubts, one could ask the patient to return for supervised evening medication administration (although this may pose logistical challenges) while the patient is wearing the monitor. Other techniques to enhance surveillance of medical compliance may be pill counts or measurement of antihypertensive medication blood levels, but these have proven unreliable or costly in our experience. The next question is are there medications or illicit drugs that may cause a blood pressure increase, and if so, can these be replaced by alternative medications? Box 22.1 provides a list of the more common medications and illicit drugs that one needs to consider. When it is determined by ambulatory blood pressure measurement that the patient indeed has resistant hypertension and after all medications or illicit drugs that may cause a high blood pressure are eliminated, the next step is an assessment for secondary hypertension. A list of the most common causes is outlined in Box 22.2. Many can be eliminated by history, physical examination (including measurement of blood pressure in both upper and lower extremities to rule out aortic coarctation and subclavian artery stenosis), and standard laboratory tests that are recommended in any patient with hypertension (including serum electrolytes [calcium included], creatinine, uric acid, complete blood count, and urinalysis

BOX 22.1 Common Substances That May Increase Blood Pressure

Alcohol
Caffeine
Selective and nonselective COX inhibitors or NSAIDs
Exogenous steroids (e.g., prednisone or oral contraceptives)
Cocaine and amphetamines
Appetite suppressants
Nasal decongestants
Licorice (including chewing tobacco)
Antidepressants
Ketoconazole
Cyclosporine
Antiemetics (e.g., metoclopramide)
Erythropoietin

COX, Cyclooxygenase; NSAID, nonsteroidal antiinflammatory drug.

BOX 22.2 Causes of Secondary Hypertension

Obstructive sleep apnea (clue: nocturnal hypertension)
Renal artery stenosis
Hyperaldosteronism
Glucocorticoid excess
Pheochromocytoma
Hyperthyroidism
Hypothyroidism
Hyperparathyroidism
Coarctation of the aorta
Chronic renal insufficiency

[including check for microalbuminuria and analysis of the urinary sediment]]. Screening for endocrine causes of secondary hypertension requires a set of laboratory tests that can easily be performed in most practices. A comprehensive discussion of endocrine hypertension is beyond the scope of this chapter, but a practical approach (and that pursued in our practice) may be the following: The patient is instructed to take 1 mg of dexamethasone orally at 11 PM and to come to the office the next morning, when plasma renin, aldosterone, cortisol, and thyroid-stimulating hormone (TSH) levels are measured (at 8 AM). In addition, 24-hour collection for urinary catecholamines and metanephrines is started. If urinary metanephrines pose a logistical challenge, alternatively, plasma metanephrines can be measured, recognizing a higher rate of false-positive results than with urinary metanephrines. The upper limit of normal for renin-aldosterone ratio is 20 to 30, and the aldosterone level is typically above 15 ng/dL with an undetectable renin concentration in primary hyperaldosteronism.¹²⁶ This ratio takes into account that plasma renin activity is measured in nanograms per milliliter, and plasma aldosterone concentration is measured in nanograms per deciliter. However, the upper normal ratio may vary if other units or assays are used as outlined by Funder et al.¹²⁶ In healthy individuals, the 8 AM cortisol level should be less than 1.8 µg/dL.¹²⁷ This cutoff provides a sensitivity of greater than 95% and a specificity of 80%.¹²⁸ The urinary catecholamines should be less than twice the upper limit of normal.¹²⁹ In the presence of a pheochromocytoma, the urinary metanephrine levels are typically significantly elevated (several-fold higher than the upper reference limit).¹²⁹ There are a few important aspects when considering endocrine secondary

hypertension. These include hyperaldosteronism, glucocorticoid excess, pheochromocytoma, and hyperparathyroidism and hyperthyroidism.

Hyperaldosteronism

The estimated prevalence rates of primary hyperaldosteronism in patients with hypertension and resistant hypertension are 5% to 12% and 23% to 26%, respectively.¹³⁰⁻¹³⁴ These estimates were lower (0.05%–2%) when hypokalemia was considered to be an essential component of hyperaldosteronism.¹³⁵ It is now recognized that most patients with primary hyperaldosteronism are, in fact, normokalemic.¹³⁶ Nevertheless, laboratory clues may include hypokalemia and a slightly increased sodium concentration. Plasma renin and aldosterone levels are measured while the patient has been sitting for at least 5 minutes in the morning and after at least 2 hours of upright posture (standing, walking, or sitting).¹²⁶ Postural maneuvers are not necessary. It is essential that the patient is normokalemic at the time of measurement because hypokalemia suppresses aldosterone secretion (potentially leading to false-negative results), and under optimal circumstances, liberal salt intake should be encouraged.¹²⁶ Although a number of medications may interfere with test accuracy, for practical purposes, all antihypertensive medications may be continued with the exception of aldosterone inhibitors (spironolactone or eplerenone) and direct renin inhibitors (e.g., aliskiren). Aldosterone inhibitors should be discontinued 6 weeks before measurement. Furthermore, chewing tobacco and licorice may affect test accuracy and must be discontinued before testing. It is best to keep in mind that most commonly used antihypertensive agents (including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and dihydropyridine calcium channel blockers) have a tendency to cause false negative results by virtue of primarily increasing the renin level. Therefore, if these agents are continued, a markedly positive test result or a renin level above the upper limit of detection is accompanied by a high likelihood of primary aldosteronism. Treatment with beta-blockers or central alpha-2 agonists (e.g., clonidine and methyldopa) may lower the plasma renin activity but also lowers plasma aldosterone concentrations, typically leaving the renin-aldosterone ratio unchanged¹³⁷; however, false-positive test results have been reported (related to a more pronounced reduction in renin levels compared with aldosterone concentration).¹³⁸ Depending on whether renin activity or concentration is measured, false-positive and false-negative results, respectively, have been reported. Hence, with regard to the aforementioned antihypertensive agents, if test results are not diagnostic, discontinuation of these medications and temporary replacement with alternative antihypertensive medications that do not interfere with testing (e.g., verapamil, hydralazine, prazosin, doxazosin, terazosin),¹²⁶ followed by test repetition can be considered. When an abnormal renin-aldosterone level is encountered, collaboration with an endocrinologist for the purpose of confirmatory tests (oral or intravenous [IV] salt loading^{126,139} or fludrocortisone stimulation¹²⁶ test) will facilitate further management. When screening and confirmatory test results are positive, most



proceed with imaging (computed tomography [CT] with protocol focusing on the adrenal gland) and adrenal vein sampling, with adrenal gland removal in case of lateralization (particularly if this corresponds with an adrenal mass). An argument can also be made to proceed with unilateral removal of the adrenal gland in young patients (younger than 40 years) who are found to have an unequivocal adrenal mass without prior adrenal vein sampling as an incidental adrenal mass (incidentaloma) is uncommon in this age category.¹⁴⁰ However, it is important to keep in mind that CT scanning alone to localize an adrenal adenoma can be misleading because misidentification is common. Adrenal vein sampling can be technically challenging, but the success rate has been reported as high as 74% to 96%.^{139,141-145} The sensitivity of adrenal vein sampling for the detection of a unilateral adrenal adenoma is 95% and 100%, respectively, and superior to CT imaging.^{141,142} Adrenal vein sampling is important because it helps to determine whether a patient has “surgical disease” (adrenal adenoma [35%] or unilateral primary adrenal hyperplasia [2%])¹⁴⁶ with a potential cure after unilateral adrenalectomy or idiopathic hyperaldosteronism (60%)¹⁴⁶ or glucocorticoid-remediable hyperaldosteronism (<3%),¹⁴⁶ both of which are treated medically. Adrenal aldosterone-producing carcinomas (<1%) and ectopic aldosterone-producing carcinomas (<0.1%) are so rare¹⁴⁶ that they are not discussed here.

What if the patient has hypertension and hypokalemia and very low renin and aldosterone concentrations? Under these circumstances, conditions that mimic hyperaldosteronism but do not cause aldosterone excess should be considered. These include exogenous administration of substances such as glucocorticoids or licorice ingestion, conditions that lead to an excess of substances with mineralocorticoid activity other than aldosterone (11-beta hydroxylase deficiency, deoxycorticosterone-producing tumors, glucocorticoid-producing tumors, congenital adrenal hyperplasia), or Liddle's syndrome caused by a sodium channel defect in the tubuloe epithelial cells leading to sodium retention and potassium wasting.

Glucocorticoid Excess

Although the most convenient screening test, especially in patients with a low clinical suspicion, is the overnight dexamethasone suppression test, alternative tests (midnight salivary cortisol [should be measured twice] and urinary free cortisol [should be measured twice]), particularly in patients with a higher degree of suspicion, are reasonable.¹²⁷ Potential pitfalls are medications that interact with the cytochrome P450 enzyme, thereby interfering with cortisol metabolism and causing false-positive or false-negative results. If feasible, these should be discontinued before testing. In patients with renal failure, dexamethasone suppression test should be preferred over urinary free cortisol.¹²⁷ In patients with suspected cyclic Cushing's syndrome, urinary free cortisol or midnight salivary cortisol are preferred over the dexamethasone suppression test.¹²⁷ In those without renal insufficiency, if urinary free cortisol is chosen as the screening test, high-performance liquid chromatography (HPLC) has a better performance than immunoassays, and the upper limit of

normal is 40 to 50 $\mu\text{g}/24$ hours with a greater than four times upper limit of normal highly suggestive of Cushing's syndrome.¹⁴⁷ If the screening test result is abnormal, it is best to collaborate with an endocrinologist for confirmatory testing and determination if the underlying problem is a pituitary adenoma (68%) or ectopic adrenocorticotrophic hormone (ACTH) syndrome (usually the consequence of small cell lung cancer [12%], adrenal adenoma [10%], or adrenal carcinoma [8%]).¹⁴⁷ Other tumors (ectopic corticotropin-releasing hormone [CRH]-secreting tumors or micronodular hyperplasia) are rare (<2%).¹⁴⁷ Under most circumstances, the next steps are brain magnetic resonance imaging, CRH stimulation test, ACTH level determination, and high-dose 48-hour dexamethasone suppression test.

Pheochromocytoma

Although pheochromocytomas are rare even in patients with resistant hypertension, screening in resistant hypertension is recommended because the consequences of a missed tumor are serious, and appropriate treatment may offer a potential cure. The use of plasma metanephrines for screening is more convenient than urinary collection; however, it is important to recognize that the specificity is limited with a false-positive rate of 15% to 25% depending on age.^{148,149} Therefore, given the rarity of this tumor, the chance that an elevated plasma metanephrine result is, in fact, related to a pheochromocytoma in a patient with a low clinical suspicion is very low. Hence, urine metanephrine collection (specificity >90%¹⁴⁸) may be a better screening test in patients with low clinical suspicion. Importantly, provided HPLC or mass spectrometry methods are used, most medications including antihypertensives can be continued¹⁵⁰ with the exception of tricyclic antidepressants and Flexeril. Measurement during major stress (e.g., critical illness, after surgery, during drug withdrawal) is not recommended (because of a high false-positive rate). It probably does not matter whether the patient is supine or upright when the blood sample is obtained.

Hyperparathyroidism and Hyperthyroidism

These conditions can easily be ruled out by including a TSH level and calcium level in the routine laboratory investigations.

What is considered to be a response to renal denervation? Several definitions have been used. The most common (used in pivotal denervation trials) is a reduction of average 24-hour ambulatory SBP of greater than 5 to 10 mm Hg.

The response rate varies somewhat by definition and concept but is typically 35% to 73%.^{116,120,151-153}

The baseline magnitude of SBP appears to be a consistent predictor of response and magnitude of response.^{152,154} The higher the initial SBP, the higher appears to be the response rate and magnitude of blood pressure reduction. Other predictors have included baseline heart rate (a heart rate >70 beats/min at baseline is associated with a better response)¹⁵⁵ and diurnal blood pressure variation,¹⁵⁶ both of which may be related to a higher baseline sympathetic tone. In addition, the presence of diastolic hypertension has been associated with a better success rate compared

with isolated systolic hypertension.¹⁵⁷ However, it is important to note that, for example, in the analysis of the combined Symplicity HTN-3 trial and registry, patients with isolated systolic hypertension also benefitted from renal denervation (albeit the response was less pronounced).¹⁵⁸ It has further been reported that patients who were taking a mineralocorticoid antagonist¹⁵² at baseline were more likely to benefit from renal denervation than those who were not, and the effect appeared to be less pronounced in patients who were treated with vasodilatory¹⁵⁹ antihypertensive agents. Finally, some data suggest that patients with increased arterial stiffness are less likely to respond. For example, in one study assessing arterial stiffness invasively before renal denervation, the reduction in 24-hour ambulatory blood pressure was more pronounced after denervation in patients with a pulse wave velocity of greater than 14.4 m/s (indicative of stiffer arteries).¹⁶⁰ In this study, logarithmic ascending aortic distensibility (measured by magnetic resonance tomography), also a parameter used to assess arterial stiffness, was a predictor of response. Nevertheless, it would be premature to exclude patients based on any of the aforementioned parameters given that the sensitivity and specificity of these parameters are limited. More so, these parameters can be helpful in educating certain patients with less favorable characteristics that the likelihood or magnitude of blood pressure reduction may be less than expected in an ideal patient.

PROCEDURE

Antiplatelet Therapy and Anticoagulation

There is no universally accepted standard protocol for renal denervation. However, endothelial injury (denudation with or without thrombus formation) or thrombus or char formation at the catheter tip is to be expected^{89,161} with the use of most current denervation technology. Therefore, although not proven, antiplatelet therapy before the procedure (e.g., 81–325 mg of aspirin or 600 mg of clopidogrel in those who are intolerant to aspirin) followed by 2 to 4 weeks of therapy (81–100 mg of aspirin or 75 mg of clopidogrel daily) to cover the presumed duration for reendothelialization and healing⁸⁹ seems to be justified (longer in the presence of other indications for antiplatelet therapy). In addition, before insertion of any equipment into the renal arteries, IV anticoagulation with heparin (goal activated clotting time >250 seconds) or bivalirudin should be performed to avoid thrombus adherent to wires or ablation equipment used for the procedure.

For most interventional cardiologists, nephrologists, and interventional radiologists, the routine performance of the procedure is not technically challenging. When challenges do occur, they are usually related to aortic or iliac tortuosity).

Access

With rare exceptions, femoral arterial access is used. An alternative access site is the brachial artery. However, given the length of the currently available, they may not reach the renal artery (depending on the patient's height

and arterial tortuosity). Standard femoral access using the Seldinger technique is performed with insertion of a sheath, the size of which depends on the denervation system used (6 Fr for the SPYRAL catheter, 7 Fr for the Recor Paradise system, and 7 Fr for the Peregrine system). In case of severe iliac tortuosity, the use of a long (e.g., 40–45 cm) sheath can be considered to reduce friction and facilitate torque transmission to the guide catheter by straightening the iliac vasculature. Device manufacturers are developing newer generation devices that will hopefully allow performance of renal denervation from the radial approach. However, more pronounced respiratory and cardiac motion via the brachial or radial approach can cause significant catheter instability and may compromise consistent wall contact.

Angiography

A pigtail or Omni Flush catheter (AngioDynamics) is advanced into the abdominal aorta over a 0.035-inch guidewire with the tip position between L1 and L2. The wire is removed, and contrast is injected (15–20 cc if digital subtraction angiography is used; 20–30 cc if conventional angiography is used). Another option preferred by the authors is to place the renal guide catheter to be used for angiography and denervation into the abdominal aorta with the tip between L1 and L2 over a 0.035-inch guidewire with injection through the guide catheter while the wire remains in the distal thoracic aorta well ahead of the guide catheter tip (this requires the use of a Y-connector before angiography) (Video 22.1). The guide catheter may then be used to perform selective angiography. A shallow (10–20 degrees) left anterior oblique projection given the typically slightly more anterior take-off of the right compared with the left renal artery is used for abdominal aortic angiography. Size, take-off, course, tortuosity, and bifurcation pattern of the renal arteries are examined, and attention is directed to the presence and size of accessory renal arteries and any significant atherosclerosis. The guide catheter is selected according to anatomy. In many cases, the renal artery take-off is slightly inferiorly oriented and the shape of an internal mammary catheter is most suitable for selective engagement. When the take-off is horizontal, a renal double curve guide catheter or a Judkins right (JR-4) may be well suited. For the (unusual) superior take-off, a multipurpose catheter may be preferred. The guide catheter may be engaged into the renal arteries directly after guidewire removal. However, we prefer the use of the “no touch technique” by which the guide catheter, with the wire still in place several centimeters ahead of the catheter tip (in the thoracic aorta), is oriented toward the renal artery ostium (small contrast injections during maneuvering can confirm optimal position) (Video 22.2). A second, smaller coronary (0.014-inch, e.g., Iron man) or peripheral (0.018-inch, e.g., Spartacore) guidewire may be advanced into the renal artery to further facilitate engagement. Subsequently, the 0.035-inch guide wire is removed, allowing the guide catheter to “fall into” or passively engage the renal artery. This may lower the risk of plaque disruption and embolization in a hostile aorta or dissection of the renal artery at engagement.



When engagement proves difficult, consideration may be given to advancing a glide wire into the renal artery as a rail for the guide catheter. For most renal denervation devices, catheter positioning 3 to 4 mm into the renal artery facilitates denervation catheter entry into the renal artery because most devices will, once they reach the catheter tip, straighten it out, causing it to point upward, roofing the renal artery and impeding further advancement. When deeper guide catheter positioning is difficult, a glide wire can first be advanced into the renal artery, and if necessary, a smaller (e.g., 4-Fr) diagnostic catheter (e.g., JR-4) is advanced through the guide catheter into the renal artery in a telescoping fashion as a rail for the guide catheter to allow deeper engagement. Selective angiography is performed (2–3 cc is typically sufficient for this purpose) with extended cine-angiographic imaging for visualization of the contrast nephrogram. Rarely, more than 10 cc is necessary for selective angiography of both renal arteries. In case of renal insufficiency, consideration may be given not to perform abdominal aortography, and selective angiography during denervation may be performed with carbon dioxide. The imaging quality is inferior to conventional angiography but sufficient to provide guidance for catheter positioning.¹⁶²

CURRENTLY COMMERCIALY AVAILABLE CATHETERS

SPYRAL Catheter System (see Figure 22.6)

Before patient draping in the catheterization laboratory, it is important to place a dispersive electrode (grounding pad) preferably to the patient's soft tissue (e.g., the inner aspect of the thigh or flank). The cable of the grounding pad must be connected to the generator. Of note, insufficient skin contact may cause burns or high catheter electrode impedance. Femoral access is obtained in the usual fashion, and aortography, renal angiography, and guide catheter (6 Fr minimum) engagement is performed as previously outlined. A Tuohy-Borst adapter is attached to the proximal end of the guide catheter and a stopcock

side arm to the Tuohy-Borst adapter. First, the renal artery is wired with a 0.014-inch guidewire (soft-tipped, nonhydrophilic guidewires are preferred to minimize inadvertent perforation of distal renal arterial branches). It is recommended that the target vessel size is 3 to 8 mm. Then the SPYRAL catheter (0.052-inch, 117-cm length) is advanced over the guidewire into the target vessel (either the main renal artery or its branches). It is helpful to use the straightening tool when loading the SPYRAL catheter onto the guidewire. Although it is advanced over the guidewire, it has not yet assumed its spiral shape and tracks the guidewire (Figure 22.11 and Video 22.3). It is important to assure that all four electrodes exit the guide catheter tip. When in the desired location, the guidewire is partially withdrawn (distal wire tip >6 cm proximal to the proximal electrode) with care taken to leave some wire within the monorail system (in this context, it is important to mention that the length of the monorail segment is 30 cm). This maneuver allows the catheter to assume its spiral shape (see Figure 22.11 and Video 22.4). Depending on the anatomy, either all four or only some electrodes will make contact with the renal artery wall. If the location is acceptable angiographically and the impedance suggests good electrode contact (~250 Ohm), then radiofrequency energy is applied. If the location of an electrode is suboptimal (e.g., it is close to more important branches such as the adrenal artery branch or ureteral arteries or the contact is poor), it can be selectively deactivated during radiofrequency energy application. Radiofrequency energy is then applied by either depressing a foot pad or pressing a button on the remote control or touch screen of the generator. The duration of the ablation is 60 seconds. If an electrode turns off prematurely, this electrode can again be turned on, remembering to deactivate the other electrodes. After ablation has been performed in one location and further ablation is desirable in a different location of the same branch or in a different branch, the guidewire can be readvanced, straightening the SPYRAL catheter and repositioning it into the desired location or branch and the catheter repositioned over the guidewire. RF energy is again

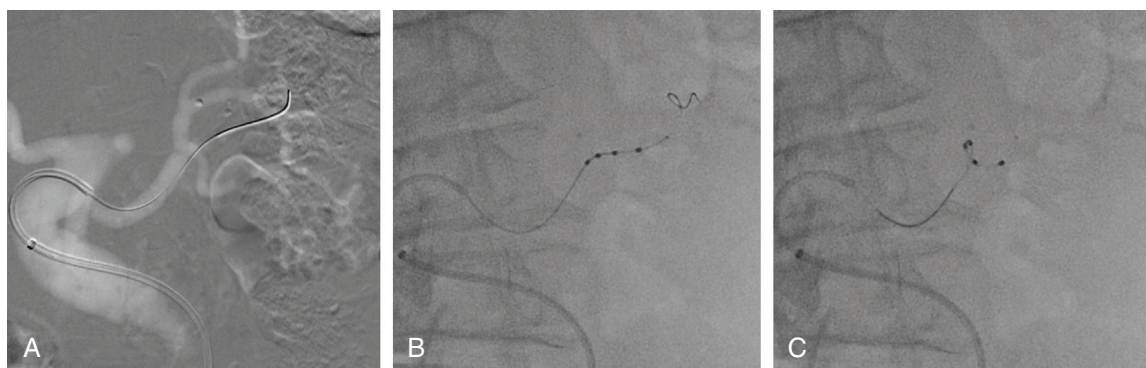


FIGURE 22.11 Carbon dioxide angiography of the left renal artery in a patient with severe aortic tortuosity. **A**, A long sheath is in place with the tip in the infrarenal abdominal aorta, and a guide catheter is engaged into the left renal artery. The left renal artery has been wired with a 0.014-inch guidewire. **B**, The SPYRAL catheter that has been advanced over the wire into the renal artery. **C**, The wire has been partially retracted with the soft tip remaining just proximal to the spiral shape of the catheter to allow the catheter to assume its spiral shape and the electrodes to establish contact with the renal artery wall.

applied. If the primary renal artery branches are of sufficient size, we recommend RF applications in these branches followed by the main renal artery because this strategy may be associated with greater blood pressure reductions.

The Recor Medical Paradise System

(see Figure 22.7)

This consists of a rapid exchange catheter (compatible with a 7-Fr guide catheter) with a distal ultrasound transducer that is engulfed in a balloon (noncompliant) irrigated with cooling fluid. This allows emission of ultrasound energy to depths of 6 mm while avoiding injury at the balloon-intima-media interface. The catheter is connected to a generator and irrigation fluid (sterile water). There are several balloon sizes from 3.0 to 8.0 mm, and the size is tailored to the diameter of the renal artery segment to be treated. The main renal artery should have at least a length of 20 mm. After femoral arterial access is obtained in the usual fashion and aortography and renal artery angiography performed, the renal artery is wired with a soft-tipped (preferably nonhydrophilic support) 0.014-inch guidewire, and the catheter is advanced over this guidewire to the desired location (>5 mm from the renal artery ostium). Catheter irrigation is initiated and ultrasound energy applied. The balloon is deflated and can be repositioned more distal or proximal in a nonoverlapping fashion in the same vessel, or it can be positioned into a branch vessel. Typically, two to four (7 seconds each) ultrasound applications are performed on each side depending on the renal arterial anatomy. Provided accessory renal arteries are larger than 3 mm in diameter, these can be safely treated.

THE PEREGRINE SYSTEM

(SEE FIGURES 22.8 AND 22.9)

This is a catheter that can be delivered through a 7-Fr guide catheter. At the catheter tip, there is a 0.014-inch floppy (atraumatic) guidewire that can be shaped to the desired shape and allows the catheter to be advanced into the renal artery. The first step is the deployment of hypotubes (required landing zone ~5 mm; Video 22.5) via manipulation of the catheter handle that serves to establish contact with the renal artery wall and, more important, center the device in the renal artery. The hypotubes and ultimately, the needles, are arranged at 120 degrees from one another. After the hypotubes are deployed in a satisfactory position, three ultra-fine needles (0.008 inch [203 μ m]) are deployed via the hypotubes and penetrate the renal artery wall protruding about 3.5 mm beyond the hypotube tips (Video 22.6 and 22.7). Then the alcohol (0.6 mL) is infused over about 60 seconds into the perivascular space. Finally, the needles and hypotubes are retracted, and the catheter is removed. It is not unusual to witness some microextravasation if angiography is performed shortly after treatment (Video 22.8); however, so far, this has not required any further intervention because all leaks have resolved during final angiography a few minutes later. The potential benefits of this concept and device are a greater

denervation depth (as demonstrated in animal models^{163,164}) compared with denervation with the single-electrode radiofrequency catheter and sparing of the intima and media from radiofrequency or ultrasound energy. It has been studied in a first-in-human single arm study demonstrating safety and efficacy¹⁶⁵ and in the European postmarket study in which 45 patients with combined hypertension underwent denervation (with 0.6 mL per renal artery).¹⁶⁶ Compared with baseline, at 6 months, there was a significant 11-mm Hg reduction in 24-hour ambulatory SBP (and a reduction in office SBP by 18 mm Hg). In addition, there was a significant reduction in diastolic 24-hour ambulatory blood pressure of 7 mm Hg. The response rate (defined as a >10-mm Hg reduction in 24-hour ambulatory blood pressure) was 52% and was 71% if it was defined as greater than 5 mm Hg. There were two guide catheter-induced renal artery dissections that were managed conservatively without sequelae, and at 6-month follow-up, there were no renal artery abnormalities seen by CT, magnetic resonance angiography (MRA), or duplex ultrasonography. These promising initial trial results prompted the performance of TARGET BP (<https://clinicaltrials.gov/ct2/show/NCT02910414?term=TARGET+BP&rank=1>) and TARGET BP OFF MED (<https://clinicaltrials.gov/ct2/show/NCT03503773?term=TARGET+BP&rank=3>) trials randomizing patients with combined hypertension to renal denervation with the Peregrine catheter or sham. Both trials are ongoing and actively enrolling at the time of this writing.

Sedation, Analgesia, and Other Necessary Medications

Routine administration of benzodiazepines (e.g., midazolam) and opioid analgesics (e.g., fentanyl or morphine) before radiofrequency or ultrasound energy application is recommended because severe visceral (abdominal, lower back, and pelvic) pain is almost always encountered with radiofrequency or ultrasound energy application. The location of pain fibers has not been well studied; however, some evidence points to the media.¹⁶⁷ Antiemetics (e.g., 1 mg of IV granisetron or 4–8 mg of IV ondansetron) are not prophylactically used but should be readily available for opioid- or pain-induced nausea. In addition, IV atropine (1 mg) should be available in case of a vagal reaction, and flumazenil and naloxone should be available to reverse respiratory depression caused by benzodiazepines and opioids.

Equipment

All the usual tools for angiography and medications that have been mentioned in this chapter should be available. In addition, bailout equipment is important. This should include stents of 4- to 7-mm diameter (the typical diameter of renal arteries) and 10- to 20-mm length as well as 0.014- or 0.018-inch guidewires (e.g., Iron Man or Spartacore, Abbott) and balloon-expandable covered stents (e.g., Atrium iCAST covered stent, Atrium) in case of renal artery perforation (no such report published to date). Necessary equipment for emergent airway management



(including for endotracheal intubation) in case of excessive sedation with respiratory compromise must be in the catheterization laboratory, and personnel trained in emergent airway management must be readily available.

EFFECT OF RENAL DENERVATION ON CONDITIONS OF SYMPATHETIC OVERACTIVITY OTHER THAN HYPERTENSION

Diabetes Mellitus and the Metabolic Syndrome

There is evidence to support that a heightened sympathetic tone may contribute to the development not only of hypertension but also obesity, insulin resistance, diabetes mellitus, and hyperlipidemia, all components of the metabolic syndrome.¹⁶⁸⁻¹⁷² Likewise, there is evidence to support that these conditions can cause a heightened sympathetic tone.¹⁷³⁻¹⁷⁵ Hence, it is plausible that renal denervation may favorably impact the above-mentioned features of the metabolic syndrome. Moxonidine, a sympathetic inhibitor, causes a reduction in glucagon secretion as well as gluconeogenesis and glycogenolysis with a reduction in glucose levels.¹⁷⁶ In patients with diabetes mellitus, improved fasting glucose, insulin levels, C-peptide levels, glucose levels after oral glucose tolerance test, and Homeostasis Assessment Model for Insulin Resistance (HOMA-IR) have been reported in a small cohort, supporting improvements in glucose control and insulin sensitivity after denervation.¹⁷⁷⁻¹⁷⁹ The physiological basis for these observations is not certain. Enhanced skeletal muscle blood flow is conceivable.¹⁸⁰ Decreases in sympathetic nervous system activity and the corresponding reduction in adrenergic alpha-1 receptor mediated vasoconstriction may improve skeletal muscle blood flow and capillary density, thereby promoting glucose transport into insulin-sensitive skeletal muscle.¹⁸¹ It must be mentioned, however, that there were no beneficial effects on insulin resistance in patients with hypertension and the metabolic syndrome in the denervation of the renal artery in metabolic syndrome (DREAMS) study.¹⁸² Twenty-nine patients were enrolled, and at 6 and 12 months, there was no difference in insulin sensitivity; however, there was also no difference in sympathetic activity measured by muscle sympathetic nerve activity. Hence, although attractive in theory and beneficial in some clinical trials, a conclusion regarding the benefits of renal denervation on metabolic parameters cannot be made.

Renal Insufficiency

Early studies have excluded patients with more than mild renal insufficiency. Hence, the safety and efficacy of renal denervation in patients with advanced renal failure are not clear. Moreover, concerns have been raised that the change in renal hemodynamics after renal denervation may accelerate renal injury. However, on theoretical grounds, renal denervation would be expected to have a favorable effect on blood pressure given the observed increase in renal and overall sympathetic nervous system activity and blood pressure demonstrated in animal models of renal

injury (attenuated by prior renal denervation)^{43,46} and pronounced increase in muscle sympathetic nerve activity, a surrogate for sympathetic nervous system activity, seen in a number of studies of patients with renal injury, including dialysis patients⁶⁸ and patients with advanced renal insufficiency,⁷⁵ polycystic kidney disease,¹⁸³ and kidney transplantation,⁶⁹ with a direct relationship between severity of renal insufficiency and muscle sympathetic nerve activity.¹⁸⁴ In neither of the Symplicity trials including patients with hypertension with normal or mildly reduced renal function at baseline, an adverse effect on renal function occurred.^{107,185} Moreover, small studies suggest the safety and efficacy of renal denervation in patients with renal insufficiency and end-stage renal disease. In one study of 15 patients with stage 3 to 4 CKD, office blood pressure reductions after renal denervation were similar to those reported in Symplicity HTN-1 and -2 with a more favorable dipping profile related to nocturnal blood pressure reductions but no significant change in average ambulatory blood pressures.¹⁸⁶ In this study, there was no deterioration of renal function up to 12 months based on serum creatinine and cystatin C and no difference in proteinuria. Furthermore, in a small ($n = 12$) study of patients with end-stage renal failure on dialysis, renal denervation could be performed without complications in 9.¹⁸⁷ Three patients' renal arteries were atrophic and of too small caliber for denervation. There were no complications suggesting that renal denervation can safely be performed in patients with end-stage renal failure. There are some data evaluating the potential benefits of a reduction in sympathetic with regard to renal function. In patients with renal insufficiency treated with moxonidine, a drug that decreases sympathetic tone, an attenuation of the decline in renal function was noted, which may have been unrelated to blood pressure-lowering effects because this medication had only a minimal effect on blood pressure.¹⁸⁸ In animal models, renal denervation has been demonstrated to cause a blood pressure reduction and slowing of a decline in renal function.^{46,189,190} In humans with renal insufficiency, a reduction in albuminuria was seen after renal denervation as well as improvements in renal function.¹⁹¹⁻¹⁹³ Certainly, to date, there are no signals that would suggest an adverse effect of renal denervation on renal function. Prospective studies with longer term follow-up will need to be performed to better evaluate a potential renal protective role.

Atrial Fibrillation

This condition has become more frequent with an aging population. Furthermore, patients with atrial fibrillation often also have concomitant hypertension. The result of pulmonary vein isolation in patients with therapy-refractory atrial fibrillation is less than ideal.¹⁹⁴ The sympathetic nervous system has an important role in the initiation and maintenance of atrial arrhythmias. A higher sympathetic tone may cause arrhythmias directly by its effect on myocytes¹⁹⁵ (e.g., enhanced automaticity, effective refractory period heterogeneity, and delayed afterdepolarization) and by ventricular or atrial remodeling caused by longstanding hypertension. Therefore, renal denervation may

have a role in patients with atrial fibrillation, both regarding arrhythmia burden and improvement in blood pressure control. A few prospective randomized trials have now demonstrated a potential benefit of renal denervation in patients with atrial fibrillation. The first controlled prospective randomized (single-center) trial was performed by Pokushalov et al.¹⁹⁶ Patients ($n = 27$) with atrial fibrillation and resistant hypertension were randomized to pulmonary vein isolation alone or combined pulmonary vein isolation and renal denervation (single-electrode Symplicity catheter with about six ablations per artery). In the group of patients that underwent both pulmonary vein isolation and renal denervation, there was a significant SBP and DBP reduction compared with baseline. However, in the group that underwent pulmonary vein isolation only, there was no significant blood pressure reduction. Sixty-nine percent of patients in the group that underwent both pulmonary vein isolation and renal denervation were free of atrial fibrillation at follow-up compared with only 29% in patients who underwent pulmonary vein isolation alone ($P = .033$). Subsequently, a small ($n = 69$) randomized trial compared pulmonary vein isolation and renal denervation with pulmonary vein isolation and spironolactone (50 mg/day) in patients with atrial fibrillation, renal insufficiency, and hypertension.¹⁹⁷ At 1-year follow-up, more (61%) patients who underwent pulmonary vein isolation and renal denervation were free of atrial fibrillation than those who underwent pulmonary vein isolation and addition of spironolactone (36%; $P = .024$). In addition, the atrial fibrillation burden was lower in patients who underwent both pulmonary vein isolation and renal denervation (-12% ; $P < .0001$). The largest trial to date is the randomized, single-blind, multicenter Renal Artery Denervation In Addition to Catheter Ablation To Eliminate Atrial Fibrillation (ERADICATE-AF) trial.¹⁹⁸ Patients ($n = 302$) with atrial fibrillation and hypertension (treated with at least one antihypertensive agent) were randomized to pulmonary vein isolation alone or pulmonary vein isolation and renal denervation using the irrigated radiofrequency catheter. At 12 months, 72% of patients treated with both pulmonary vein isolation and renal denervation were free of atrial fibrillation, flutter, and tachycardia compared with 57% of patients who underwent pulmonary vein isolation alone ($P = .006$). In addition, in patients who underwent pulmonary vein isolation and renal denervation, the mean SBP was 13 mm Hg lower than that seen in patients who underwent pulmonary vein isolation alone. A meta-analysis of trials examining the benefit of renal denervation in addition to atrial fibrillation ablation demonstrated a reduction in atrial fibrillation burden when both procedures were combined compared with pulmonary vein isolation alone.¹⁹⁹ Finally, the small ($n = 20$), single-center Atrial fibrillation reduction by renal sympathetic denervation (AFFORD) trial assessed the impact of renal denervation on atrial fibrillation burden in patients with atrial fibrillation and hypertension.²⁰⁰ The atrial fibrillation burden was measured using an implantable cardiac monitor and diminished after renal denervation from 1.39 min/day before renal denervation to 0.94 min/day at 12 months ($P = .03$). Given the aforementioned data, it appears likely that renal denervation in addition to pulmonary vein isolation may

be more effective in preventing atrial fibrillation recurrences and may reduce atrial fibrillation burden compared with pulmonary vein isolation alone in patients with atrial fibrillation and hypertension. It is worth mentioning the randomized Symplicity Atrial fibrillation (AF) trial comparing cryoablation for atrial fibrillation with cryoablation and renal denervation using the SPYRAL catheter in patients with atrial fibrillation (paroxysmal or persistent) and hypertension. Enrollment has been completed, and results are expected in 2022.

Ventricular Arrhythmias

Sympathetic nervous system activity has been implicated in the generation of ventricular arrhythmias. A natural experiment that illustrates the role of the sympathetic nervous system is cardiac transplantation. After cardiac transplantation, ventricular arrhythmias are uncommon,²⁰¹ and when they occur, they are usually related to acute ischemia or rejection.²⁰² Some animal studies support the potential antiarrhythmic effect of sympathetic denervation. In models in which acute ischemia is triggered by left anterior descending coronary artery ligation, animals that underwent renal sympathetic denervation were less prone to ventricular arrhythmias than control animals.^{203,204} Currently, no prospective randomized trials have evaluated the utility of renal denervation in patients with ventricular arrhythmias. Nevertheless, there are a number of case reports and case series of patients with ventricular arrhythmias refractory to conventional therapies (including antiarrhythmics and catheter-based ablations) in whom renal denervation reduced the arrhythmic burden significantly.²⁰⁵⁻²¹⁰ It is, in this context, also worthwhile mentioning that direct cardiac sympathetic denervation (e.g., epidural anesthesia, surgical left cardiac sympathetic denervation, or stellate ganglion blockade) has been demonstrated to have a favorable impact on refractory ventricular arrhythmias.²¹¹⁻²¹⁵

Obstructive Sleep Apnea

Hypertension and antihypertensive drug resistance are very common in patients with OSA.²¹⁶ OSA causes an activation of the sympathetic nervous system,²¹⁷⁻²²¹ and activation of the sympathetic nervous system contributes to sodium and water retention, potentially exacerbating airway obstruction. Therefore, a favorable effect of renal denervation on hypertension associated with OSA and on the severity of OSA is conceivable. Some animal data and two human studies support this hypothesis. In one study of patients with sleep apnea ($n = 10$, the majority with OSA), renal denervation caused a significant and pronounced reduction in office SBP and DBP at 3 and 6 months.¹⁷⁹ There was a trend toward a reduction in the apnea-hypopnea index (16.3 events/h before denervation and 4.5 events/h after denervation; $P = .059$). In patients (8 of 10) who experienced an improvement in apnea-hypopnea index, there was a significant reduction in day- and nighttime ambulatory blood pressure ($-8/4$ mm Hg and $-12/5$ mm Hg for day- and nighttime, respectively). In addition, a significant reduction in blood glucose levels 2 hours



after glucose administration and hemoglobin A_{1c} level occurred. In another randomized trial of patients with OSA and hypertension ($n = 60$), in patients who underwent renal denervation, there was a significant reduction in ambulatory blood pressure as well as the apnea-hypopnea index (39.4 events/h to 31.2 events/h; $P = .015$).²²² However, in this study, no effect on metabolic parameters was found.

Finally, beneficial effects of renal denervation in patients with heart failure may be expected. Sympathetic overactivity is common in patients with heart failure²²³ and is associated with increased mortality rates.²²⁴ A mortality rate reduction with beta-adrenoreceptor and renin-angiotensin system inhibition has been shown in large clinical trials.^{225,226} Given the favorable effects on sympathetic tone, similar beneficial effects would be expected after renal denervation. In this context, decreased left ventricular filling pressures and improved left ventricular systolic function have been demonstrated after renal denervation in an animal model.²²⁷ The feasibility and safety of renal denervation was explored in a small ($n = 7$) pilot study. No adverse effects occurred, and functional class improved.²²⁸ A randomized trial in patients ($n = 60$) with chronic systolic heart failure demonstrated a reduction in brain natriuretic peptide levels and improved functional status and ejection fraction.²²⁹ This was accompanied by a blood pressure reduction but no symptomatic hypotension. Furthermore, renal denervation has been studied in patients with cardiomyopathy from Chagas disease without any relevant safety events, and other data suggest a potential antiinflammatory effect.²³⁰ Nevertheless, final conclusions regarding the benefits and risks of renal denervation in a heart failure population cannot be made. Ongoing studies may further clarify the role of renal denervation in this patient population.

SYMPATHETIC NERVE ACTIVITY MAPPING AND TAILORED ABLATION

It is important to note that many different types of nerves course alongside the renal artery, including efferent sympathetic fibers as well as sensory fibers and parasympathetic fibers. In this context, it is conceivable that in some areas adjacent to the renal artery, there may be an abundance of nerve fibers, the stimulation of which may lead to no effect ("neutral spots"), a blood pressure decrease ("cold spots"), or a blood pressure increase ("hot spots"), and that ablation of neutral spots and cold spots may have no effect or can cause an inadvertent increase in blood pressure. This concept has been supported by more recent (mainly animal) data suggesting that mapping of the renal artery for hot spots and limiting ablation to these sites may be accompanied by a greater success rate.^{231,232}

CONCLUSIONS

Renal activity and overall sympathetic nervous system activity play important roles in development and maintenance of hypertension and other conditions. Several

animal experiments and human observations support a potential role for renal denervation in hypertension and perhaps other conditions associated with sympathetic overactivity. In addition, early experiences with the Symplicity catheter and other novel approaches support a blood pressure-lowering effect. Temporarily, enthusiasm for the concept of renal denervation was dampened by the results of the Symplicity HTN-3 trial, and the procedure remains investigational in the United States, though it continued to be widely available in other parts of the world. Three newer generation devices have become commercially available in Europe, two of which have undergone rigorous randomized sham controlled trials demonstrating a benefit of renal denervation compared with sham. The blood pressure lowering effect appears to be lasting. Other randomized sham controlled trials are ongoing. At least for the patient population studied in the aforementioned trials (predominantly patients ~50 years of age with combined hypertension), renal denervation appears effective and should be considered, particularly in patients in whom the blood pressure is difficult to control. Although patients should not be excluded from renal denervation based on a single clinical parameter, several clinical and blood pressure characteristics appear to help predict a response and may help in patient selection. Some concepts address the possibility of mapping the renal artery to identify areas where ablation may be more likely to be accompanied by a blood pressure reduction. Some evidence supports a potential role for renal denervation in patients with atrial fibrillation and ventricular arrhythmias.

Most frequently, hypertension is asymptomatic. The treatment rationale is cardiovascular risk reduction. Therefore, ideally, establishment of any (medical or device) treatment modality in our armamentarium should be based on demonstration of a reduction in major adverse cardio- and cerebrovascular events. Hopefully, long enough follow-up of existent trials will allow us to assess if a benefit in these outcomes is likely.

REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365:217-223.
2. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *JAMA*. 2010;303:2043-2050.
3. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903-1913.
4. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA*. 2003;289:2534-2544.
5. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA*. 1997;277:739-745.
6. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation*. 2008;117:e510-e526.
7. Garg JP, Elliott WJ, Folker A, Izhar M, Black HR. Resistant hypertension revisited: a comparison of two university-based cohorts. *Am J Hypertens*. 2005;18:619-626.
8. Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens (Greenwich)*. 2002;4:393-404.

9. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417-2428.
10. Gupta AK, Nasothimiou EG, Chang CL, Sever PS, Dahlöf B, Poulter NR. Baseline predictors of resistant hypertension in the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT): a risk score to identify those at high-risk. *J Hypertens*. 2011;29:2004-2013.
11. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. *Hypertension*. 2011;57:1076-1080.
12. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation*. 2012;125:1635-1642.
13. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. *Circulation*. 2011;124:1046-1058.
14. Bertog SC, Sobotka PA, Sievert H. Renal denervation for hypertension. *JACC Cardiovasc Interv*. 2012;5:249-258.
15. Rettig R. Does the kidney play a role in the aetiology of primary hypertension? Evidence from renal transplantation studies in rats and humans. *J Hum Hypertens*. 1993;7:177-180.
16. Roman RJ, Cowley AW Jr. Characterization of a new model for the study of pressure-natriuresis in the rat. *Am J Physiol*. 1985;248:F190-F198.
17. Cowley AW Jr. Long-term control of arterial blood pressure. *Physiol Rev*. 1992;72:231-300.
18. Barajas L. The innervation of the juxtaglomerular apparatus. An electron microscopic study of the innervation of the glomerular arterioles. *Lab Invest*. 1964;13:916-929.
19. Ljungqvist A, Wagermark J. The adrenergic innervation of intrarenal glomerular and extra-glomerular circulatory routes. *Nephron*. 1970;7:218-229.
20. Muller J, Barajas L. Electron microscopic and histochemical evidence for a tubular innervation in the renal cortex of the monkey. *J Ultrastruct Res*. 1972;41:533-549.
21. Barajas L, Wang P. Localization of tritiated norepinephrine in the renal arteriolar nerves. *Anat Rec*. 1979;195:525-534.
22. Drexel T, Bertog SC, Vaskelyte L, Sievert H. Renal denervation. *Anadolu Kardiyol Derg*. 2014;14:186-191.
23. Insel PA, Snively MD, Healy DP, Munzel PA, Potenza CL, Nord EP. Radioligand binding and functional assays demonstrate postsynaptic alpha 2-receptors on proximal tubules of rat and rabbit kidney. *J Cardiovasc Pharmacol*. 1985;7(suppl 8):S9-S17.
24. Meister B, Dagerlind A, Nicholas AP, Hokfelt T. Patterns of messenger RNA expression for adrenergic receptor subtypes in the rat kidney. *J Pharmacol Exp Ther*. 1994;268:1605-1611.
25. Ibarra F, Aperia A, Svensson LB, Eklöf AC, Greengard P. Bidirectional regulation of Na⁺/K⁺-ATPase activity by dopamine and an alpha-adrenergic agonist. *Proc Natl Acad Sci U S A*. 1993;90:21-24.
26. Holtback U, Ohtomo Y, Forberg P, Sahlgren B, Aperia A. Neuropeptide Y shifts equilibrium between alpha- and beta-adrenergic tonus in proximal tubule cells. *Am J Physiol*. 1998;275:F1-F7.
27. Aldehni F, Tang T, Madsen K, et al. Stimulation of renin secretion by catecholamines is dependent on adenylyl cyclases 5 and 6. *Hypertension*. 2011;57:460-468.
28. Tomaschitz A, Pilz S, Ritz E, Obermayer-Pietsch B, Pieber TR. Aldosterone and arterial hypertension. *Nat Rev Endocrinol*. 2010;6:83-93.
29. Duprez DA. Role of the renin-angiotensin-aldosterone system in vascular remodeling and inflammation: a clinical review. *J Hypertens*. 2006;24:983-991.
30. Schiffrin EL. Effects of aldosterone on the vasculature. *Hypertension*. 2006;47:312-318.
31. Hwang KC, Gray CD, Sweet WE, Moravec CS, Im MJ. Alpha 1-adrenergic receptor coupling with Gh in the failing human heart. *Circulation*. 1996;94:718-726.
32. Berridge MJ. Inositol trisphosphate and diacylglycerol as second messengers. *Biochem J*. 1984;220:345-360.
33. Kopp UC. Role of renal sensory nerves in physiological and pathophysiological conditions. *Am J Physiol Regul Integr Comp Physiol*. 2015;308:R79-R95.
34. Marfurt CF, Echtenkamp SF. Sensory innervation of the rat kidney and ureter as revealed by the anterograde transport of wheat germ agglutinin-horseradish peroxidase (WGA-HRP) from dorsal root ganglia. *J Comp Neurol*. 1991;311:389-404.
35. Kopp UC, Cicha MZ, Smith LA, Mulder J, Hokfelt T. Renal sympathetic nerve activity modulates afferent renal nerve activity by PGE2-dependent activation of alpha1- and alpha2-adrenoceptors on renal sensory nerve fibers. *Am J Physiol Regul Integr Comp Physiol*. 2007;293:R1561-R1572.
36. Kopp UC, Grisk O, Cicha MZ, et al. Dietary sodium modulates the interaction between efferent renal sympathetic nerve activity and afferent renal nerve activity: role of endothelin. *Am J Physiol Regul Integr Comp Physiol*. 2009;297:R337-R351.
37. Ditting T, Ties G, Rodionova K, et al. Do distinct populations of dorsal root ganglion neurons account for the sensory peptidergic innervation of the kidney? *Am J Physiol Renal Physiol*. 2009;297:F1427-F1434.
38. Tyshynsky R, van Helden D, Larson E, et al. SPARC: anatomical analysis and optogenetic stimulation of TRPV1+ sensory fibers in the renal cortex. *FASEB J*. 2020;34:1.
39. Ciriello J, de Oliveira CV. Renal afferents and hypertension. *Curr Hypertens Rep*. 2002;4:136-142.
40. Ciriello J, Calaresu FR. Central projections of afferent renal fibers in the rat: an anterograde transport study of horseradish peroxidase. *J Auton Nerv Syst*. 1983;8:273-285.
41. Rosas-Arellano MP, Solano-Flores LP, Ciriello J. c-Fos induction in spinal cord neurons after renal arterial or venous occlusion. *Am J Physiol*. 1999;276:R120-R127.
42. Smits JF, Brody MJ. Activation of afferent renal nerves by intrarenal bradykinin in conscious rats. *Am J Physiol Integr Comp Physiol*. 2017;2476:R1003-R1008.
43. Ye S, Zhong H, Yanamadala V, Campese VM. Renal injury caused by intrarenal injection of phenol increases afferent and efferent renal sympathetic nerve activity. *Am J Hypertens*. 2002;15:717-724.
44. Katholi RE, Whitlow PL, Winternitz SR, Oparil S. Importance of the renal nerves in established two-kidney, one clip Goldblatt hypertension. *Hypertension*. 1982;4:166-174.
45. Katholi RE, Winternitz SR, Oparil S. Decrease in peripheral sympathetic nervous system activity following renal denervation or unclipping in the one-kidney one-clip Goldblatt hypertensive rat. *J Clin Invest*. 1982;69:55-62.
46. Campese VM, Kogosov E. Renal afferent denervation prevents hypertension in rats with chronic renal failure. *Hypertension*. 1995;25:878-882.
47. Muller E, Petersen W. Ueber den Anteil des vegetativen Nervensystems an dem Infektionsschaden der Nierengefäesse. *Verh Dtsch Ges Inn Med*. 1932;44:419.
48. Page IH, Heuer GJ. The effect of renal denervation on patients suffering from nephritis. *J Clin Invest*. 1935;14:443-458.
49. Veelen R, Vogel EM, Hilgers K, et al. Autonomic renal denervation ameliorates experimental glomerulonephritis. *J Am Soc Nephrol*. 2008;19:1371-1388.
50. Kim J, Padanilam BJ. Renal nerves drive interstitial fibrogenesis in obstructive nephropathy. *J Am Soc Nephrol*. 2013;24:229-242.
51. Banek CT, Knuepfer MM, Foss JD, et al. Resting afferent renal nerve discharge and renal inflammation: elucidating the role of afferent and efferent renal nerves in deoxycorticosterone acetate salt hypertension. *Hypertension*. 2016;68:1415-1423.
52. Kottke FJ, Kubicek WG, Visscher MB. The production of arterial hypertension by chronic renal artery-nerve stimulation. *Am J Physiol*. 1945;145:38-47.
53. Bernard C. Lecons sur les Proprietes et les Alterations Pathologiques des Liquides de l'Organisme. *Bailliers et Fils*. 1859;2:170-171.
54. Thoren P. Efferent renal nerve traffic in the spontaneously hypertensive rat. *Clin Exp Hypertens A*. 1987;9(suppl 1):259-279.
55. Abramczyk P, Zwolinska A, Oficjalski P, Przybylski J. Kidney denervation combined with elimination of adrenal-renal portal circulation prevents the development of hypertension in spontaneously hypertensive rats. *Clin Exp Pharmacol Physiol*. 1999;26:32-34.
56. Norman RA Jr, Dzielak DJ. Role of renal nerves in onset and maintenance of spontaneous hypertension. *Am J Physiol*. 1982;243:H284-H288.
57. DiBona GF, Esler M. Translational medicine: the antihypertensive effect of renal denervation. *Am J Physiol Regul Integr Comp Physiol*. 2010;298:R245-R253.
58. Anderson EA, Sinkey CA, Lawton WJ, Mark AL. Elevated sympathetic nerve activity in borderline hypertensive humans. Evidence from direct intraneural recordings. *Hypertension*. 1989;14:177-183.
59. Esler M, Jennings G, Biviano B, Lambert G, Hasking G. Mechanism of elevated plasma noradrenaline in the course of essential hypertension. *J Cardiovasc Pharmacol*. 1986;8(suppl 5):S39-S43.
60. Goldstein DS. Plasma catecholamines and essential hypertension. An analytical review. *Hypertension*. 1983;5:86-99.
61. Esler M, Jennings G, Lambert G, Meredith I, Horne M, Eisenhofer G. Overflow of catecholamine neurotransmitters to the circulation: source, fate, and functions. *Physiol Rev*. 1990;70:963-985.
62. Esler M, Lambert G, Jennings G. Regional norepinephrine turnover in human hypertension. *Clin Exp Hypertens A*. 1989;11(suppl 1):75-89.
63. Schlaich MP, Lambert E, Kaye DM, et al. Sympathetic augmentation in hypertension: role of nerve firing, norepinephrine reuptake, and Angiotensin neuromodulation. *Hypertension*. 2004;43:169-175.
64. Smith PA, Graham LN, Mackintosh AF, Stoker JB, Mary DA. Relationship between central sympathetic activity and stages of human hypertension. *Am J Hypertens*. 2004;17:217-222.
65. Grassi G, Seravalle G, Colombo M, et al. Body weight reduction, sympathetic nerve traffic, and arterial baroreflex in obese normotensive humans. *Circulation*. 1998;97:2037-2042.
66. Narkiewicz K, Pesek CA, Kato M, Phillips BG, Davison DE, Somers VK. Baroreflex control of sympathetic nerve activity and heart rate in obstructive sleep apnea. *Hypertension*. 1998;32:1039-1043.
67. Zoccali C, Mallamaci F, Parlongo S, et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation*. 2002;105:1354-1359.
68. Converse RL Jr, Jacobsen TN, Toto RD, et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med*. 1992;327:1912-1918.
69. Hausberg M, Kosch M, Harmelink P, et al. Sympathetic nerve activity in end-stage renal disease. *Circulation*. 2002;106:1974-1979.
70. Ask-Upmark. Ueber juvenile maligne Nephrosklerose und ihr Verhaeltnis zu Störungen in der Nierenentwicklung [Juvenile malignant nephrosclerosis and its role in disorders in kidney development]. *Acta Pathol Microbiol Scand*. 1929;6:383-342.
71. Butler AM. Chronic pyelonephritis and arterial hypertension. *J Clin Invest*. 1937;16:889-897.
72. Smith HW. Hypertension and urologic disease. *Am J Med*. 1948;4:724-743.
73. Cohen SL. Hypertension in renal transplant recipients: role of bilateral nephrectomy. *Br Med J*. 1973;3:78-81.
74. McHugh MI, Tanboga H, Marcen R, Liano F, Robson V, Wilkinson R. Hypertension following renal transplantation: the role of the host's kidney. *Q J Med*. 1980;49:395-403.

75. Ligtner G, Blankstijn PJ, Oey PL, et al. Reduction of sympathetic hyperactivity by enalapril in patients with chronic renal failure. *N Engl J Med*. 1999;340:1321-1328.
76. Miyajima E, Yamada Y, Yoshida Y, et al. Muscle sympathetic nerve activity in renovascular hypertension and primary aldosteronism. *Hypertension*. 1991;17:1057-1062.
77. Perry CB. Malignant hypertension cured by unilateral nephrectomy. *Br Heart J*. 1945;7:139-142.
78. Allen EV. Sympathectomy for essential hypertension. *Circulation*. 1952;6:131-140.
79. Smithwick RH, Thompson JE. Splanchnicectomy for essential hypertension; results in 1,266 cases. *JAMA*. 1953;152:1501-1504.
80. Newcombe CP, Shucksmith HS, Suffern WS. Sympathectomy for hypertension; follow-up of 212 patients. *Br Med J*. 1959;1:142-144.
81. Grimson KS, Orgain ES, Anderson B, D'Angelo GJ. Total thoracic and partial to total lumbar sympathectomy, splanchnicectomy and celiac ganglionectomy for hypertension. *Ann Surg*. 1953;138:532-547.
82. Peet MM, Isberg EM. The surgical treatment of essential hypertension. *JAMA*. 1946;130:467-473.
83. Hinton JW. End results of thoracolumbar sympathectomy for advanced essential hypertension. *Bull N Y Acad Med*. 1948;24:239-252.
84. Evelyn KA, Alexander F, Cooper SR. Effect of sympathectomy on blood pressure in hypertension; a review of 13 years' experience of the Massachusetts General Hospital. *JAMA*. 1949;140:592-602.
85. Hammarstrom S, Bechgaard P. Prognosis in arterial hypertension; comparison between 251 patients after sympathectomy and selected series of 435 non-operated patients. *Am J Med*. 1950;8:53-56.
86. Peet M, Woods P, Braden S. The surgical treatment of hypertension: results in 350 consecutive cases treated by bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic gangliectomy. Clinical lecture at the New York Session. *JAMA*. 1940;115:1875-1885.
87. Smithwick RH. Surgery in hypertension. *Lancet*. 1948;2:65.
88. Grimson KS, Orgain ES, Anderson B, Broome RA, Longino FH. Results of treatment of patients with hypertension by total thoracic and partial to total lumbar sympathectomy, splanchnicectomy and celiac ganglionectomy. *Ann Surg*. 1949;129:850-871.
89. Steigerwald K, Titova A, Malle C, et al. Morphological assessment of renal arteries after radiofrequency catheter-based sympathetic denervation in a porcine model. *J Hypertens*. 2012;30:2230-2239.
90. Rippey MK, Zarins D, Barman NC, Wu A, Duncan KL, Zarins CK. Catheter-based renal sympathetic denervation: chronic preclinical evidence for renal artery safety. *Clin Res Cardiol*. 2011;100:1095-1101.
91. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*. 2009;373:1275-1281.
92. Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic nerve ablation for uncontrolled hypertension. *N Engl J Med*. 2009;361:932-934.
93. Hering D, Lambert EA, Marusic P, et al. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. *Hypertension*. 2013;61:457-464.
94. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension*. 2011;57:911-917.
95. Krum H, Schlaich MP, Sobotka PA, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet*. 2014;383:622-629.
96. Symplicity HTN1, Esler MD, Krum H, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet*. 2010;376:1903-1909.
97. Whitbourn R. Persistent and safe blood pressure lowering effects of renal artery denervation: three year follow-up from the Symplicity HTN-2 randomized controlled trial. *Transcatheter Cardiovascular Therapeutics (TCT)*; 2013.
98. Kaltenbach B, Franke J, Bertog SC, Steinberg DH, Hofmann I, Sievert H. Renal sympathetic denervation as second-line therapy in mild resistant hypertension: a pilot study. *Catheter Cardiovasc Interv*. 2013;81:335-339.
99. Ott C, Mahfoud F, Schmid A, et al. Renal denervation in moderate treatment-resistant hypertension. *J Am Coll Cardiol*. 2013;62:1880-1886.
100. Robbins IM, Colvin EV, Doyle TP, et al. Pulmonary vein stenosis after catheter ablation of atrial fibrillation. *Circulation*. 1998;98:1769-1775.
101. Kaltenbach B, Id D, Franke JC, et al. Renal artery stenosis after renal sympathetic denervation. *J Am Coll Cardiol*. 2012;60:2694-2695.
102. Vonend O, Antoch G, Rump LC, Blondin D. Secondary rise in blood pressure after renal denervation. *Lancet*. 2012;380:778.
103. Zeller T. Percutaneous Renal Denervation System. The new ultrasound solution for the management of hypertension. *Transcatheter Cardiovascular Therapeutics*; 2013.
104. Kaye DM, Esler M, Kingwell B, McPherson G, Esmore D, Jennings G. Functional and neurochemical evidence for partial cardiac sympathetic reinnervation after cardiac transplantation in humans. *Circulation*. 1993;88:1110-1118.
105. Gazdar AF, Dammin GJ. Neural degeneration and regeneration in human renal transplants. *N Engl J Med*. 1970;283:222-224.
106. Hansen JM, Abildgaard U, Fogh-Andersen N, et al. The transplanted human kidney does not achieve functional reinnervation. *Clin Sci*. 1984;87:13-20.
107. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370:1393-1401.
108. Bhatt DL, Vaduganathan M, Kandzari DE, et al. Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPPLICITY HTN-3 Trial. *Lancet*. 2022;400(10361):1405-1416.
109. Bohm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet*. 2020;395:1444-1451.
110. Townsend RR, Mahfoud F, Kandzari DE, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet*. 2017;390:2160-2170.
111. Kandzari DE, Bohm M, Mahfoud F, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet*. 2018;391:2346-2355.
112. Mahfoud F, Kandzari DE, Kario K, et al. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. *Lancet*. 2022;399(10333):1401-1410.
113. Mabin T, Sapoval M, Cabane V, Stemmett J, Iyer M. First experience with endovascular ultrasound renal denervation for the treatment of resistant hypertension. *EuroIntervention*. 2012;8:57-61.
114. Daemen J, Mahfoud F, Kuck KH, et al. Safety and efficacy of endovascular ultrasound renal denervation in resistant hypertension: 12-month results from the ACHIEVE study. *J Hypertens*. 2019;37:1906-1912.
115. Montalescot G, Cluzel P, Girerd X, Pathak A. REALISE Trial. Renal denervation by ultrasound transcatheter emission: six month results. *J Am Coll Cardiol*. 2014;64(11):B122-B123.
116. Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet*. 2018;391:2335-2345.
117. Azizi M, Schmieder RE, Mahfoud F, et al. Six-month results of treatment-blinded medication titration for hypertension control following randomization to endovascular ultrasound renal denervation or a sham procedure in the RADIANCE-HTN SOLO trial. *Circulation*. 2019. In press.
118. Azizi M, Daemen J, Lobo MD, et al. 12-month results from the unblinded phase of the RADIANCE-HTN SOLO Trial of Ultrasound Renal Denervation. *JACC Cardiovasc Interv*. 2020;13:2922-2933.
119. Mahfoud F, Bloch MJ, Azizi M, et al. Changes in blood pressure after cross-over to ultrasound renal denervation in patients initially treated with sham in the RADIANCE-HTN SOLO trial. *EuroIntervention*. 2021;17:e1024-e1032.
120. Fengler K, Rommel KP, Lapusca R, et al. Renal denervation in isolated systolic hypertension using different catheter techniques and technologies. *Hypertension*. 2019;74:341-348.
121. Saranathan M, Bayram E, Worters PW, Glockner JF. A 3D balanced-SSFP Dixon technique with group-encoded k-space segmentation for breath-held non-contrast-enhanced MR angiography. *Magn Reson Imaging*. 2012;30:158-164.
122. Khoo MM, Deeab D, Gedroyc WM, Duncan N, Taube D, Dick EA. Renal artery stenosis: comparative assessment by unenhanced renal artery MRA versus contrast-enhanced MRA. *Eur Radiol*. 2011;21:1470-1476.
123. Shonai T, Takahashi T, Ikeguchi H, Miyazaki M, Amano K, Yui M. Improved arterial visibility using short-tau inversion-recovery (STIR) fat suppression in non-contrast-enhanced time-spatial labeling inversion pulse (Time-SLIP) renal MR angiography (MRA). *J Magn Reson Imaging*. 2009;29:1471-1477.
124. Wilson GJ, Maki JH. Non-contrast-enhanced MR imaging of renal artery stenosis at 1.5 tesla. *Magn Reson Imaging Clin N Am*. 2009;17:13-27.
125. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans: an AHA scientific statement from the Council on High Blood Pressure Research Professional and Public Education Subcommittee. *J Clin Hypertens (Greenwich)*. 2005;7:102-109.
126. Funder JW, Carey RM, Fardella C, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2008;93:3266-3281.
127. Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93:1526-1540.
128. Wood PJ, Barth JH, Freedman DB, Perry L, Sheridan B. Evidence for the low dose dexamethasone suppression test to screen for Cushing's syndrome—recommendations for a protocol for biochemistry laboratories. *Ann Clin Biochem*. 1997;34(Pt 3):222-229.
129. Kudva YC, Sawka AM, Young WF Jr. Clinical review 164: the laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience. *J Clin Endocrinol Metab*. 2003;88:4533-4539.
130. Gordon RD, Stowasser M, Tunny TJ, Klemm SA, Rutherford JC. High incidence of primary aldosteronism in 199 patients referred with hypertension. *Clin Exp Pharmacol Physiol*. 1994;21:315-318.
131. Loh KC, Koay ES, Khaw MC, Emmanuel SC, Young WF Jr. Prevalence of primary aldosteronism among Asian hypertensive patients in Singapore. *J Clin Endocrinol Metab*. 2000;85:2854-2859.
132. Young WF Jr. Primary aldosteronism: a common and curable form of hypertension. *Cardiol Rev*. 1999;7:207-214.
133. Stowasser M. Primary aldosteronism: rare bird or common cause of secondary hypertension? *Curr Hypertens Rep*. 2001;3:230-239.

134. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P. Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension*. 2002;40:892-896.
135. Young WF Jr. Endocrine hypertension: then and now. *Endocr Pract*. 2010;16:888-902.
136. Mulatero P, Stowasser M, Loh KC, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. *J Clin Endocrinol Metab*. 2004;89:1045-1050.
137. Ahmed AH, Gordon RD, Taylor P, Ward G, Pimenta E, Stowasser M. Effect of atenolol on aldosterone/renin ratio calculated by both plasma Renin activity and direct Renin concentration in healthy male volunteers. *J Clin Endocrinol Metab*. 2010;95:3201-3206.
138. Seifarth C, Trenkel S, Schobel H, Hahn EG, Hensen J. Influence of antihypertensive medication on aldosterone and renin concentration in the differential diagnosis of essential hypertension and primary aldosteronism. *Clin Endocrinol (Oxf)*. 2002;57:457-465.
139. Young WF Jr, Klee GG. Primary aldosteronism. Diagnostic evaluation. *Endocrinol Metab Clin North Am*. 1988;17:367-395.
140. Young WF Jr, Hogan MJ. Renin-independent hypermineralocorticoidism. *Trends Endocrinol Metab*. 1994;5:97-106.
141. Young WF, Stanson AW, Thompson GB, Grant CS, Farley DR, van Heerden JA. Role for adrenal venous sampling in primary aldosteronism. *Surgery*. 2004;136:1227-1235.
142. Nwariaku FE, Miller BS, Auchus R, et al. Primary hyperaldosteronism: effect of adrenal vein sampling on surgical outcome. *Arch Surg*. 2006;141:497-502; discussion 503.
143. Daunt N. Adrenal vein sampling: how to make it quick, easy, and successful. *Radiographics*. 2005;25(suppl 1):S143-S158.
144. Stowasser M, Gordon RD. Familial hyperaldosteronism. *J Steroid Biochem Mol Biol*. 2001;78:215-229.
145. Doppman JL, Gill JR Jr. Hyperaldosteronism: sampling the adrenal veins. *Radiology*. 1996;198:309-312.
146. Young WF. Primary aldosteronism: renaissance of a syndrome. *Clin Endocrinol (Oxf)*. 2007;66:607-618.
147. Findling JW, Raff H. Cushing's syndrome: important issues in diagnosis and management. *J Clin Endocrinol Metab*. 2006;91:3746-3753.
148. Young WF Jr. Adrenal causes of hypertension: pheochromocytoma and primary aldosteronism. *Rev Endocr Metab Disord*. 2007;8:309-320.
149. Singh RJ. Advances in metanephre testing for the diagnosis of pheochromocytoma. *Clin Lab Med*. 2004;24:85-103.
150. Perry CG, Sawka AM, Singh R, Thabane L, Bajnarek J, Young WF Jr. The diagnostic efficacy of urinary fractionated metanephres measured by tandem mass spectrometry in detection of pheochromocytoma. *Clin Endocrinol (Oxf)*. 2007;66:703-708.
151. Rosa J, Widimsky P, Tousek P, et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. *Hypertension*. 2015;65:407-413.
152. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370:1393-1401.
153. Azizi M, Sapoval M, Gosse P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet*. 2015;385:1957-1965.
154. Bohm M, Mahfoud F, Ukena C, et al. First report of the Global SYMPPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. *Hypertension*. 2015;65:766-774.
155. Bohm M, Tsioufis K, Kandzari DE, et al. Effect of heart rate on the outcome of renal denervation in patients with uncontrolled hypertension. *J Am Coll Cardiol*. 2021;78:1028-1038.
156. Gosse P, Cremer A, Kirtane AJ, et al. Ambulatory blood pressure monitoring to predict response to renal denervation: a post hoc analysis of the RADIANCE-HTN SOLO study. *Hypertension*. 2021;77:529-536.
157. Saxena M, Schmieder RE, Kirtane AJ, et al. Predictors of blood pressure response to ultrasound renal denervation in the RADIANCE-HTN SOLO study. *J Hum Hypertens*. 2022;36(7):629-639.
158. Mahfoud F, Bakris G, Bhatt DL, et al. Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: data from SYMPPLICITY HTN-3 and the Global SYMPPLICITY Registry. *Eur Heart J*. 2017;38:93-100.
159. Mahfoud F, Bohm M, Schmieder R, et al. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPPLICITY Registry. *Eur Heart J*. 2019;40:3474-3482.
160. Fengler K, Rommel K-P, Kriesse W, et al. Assessment of arterial stiffness to predict blood pressure response to renal sympathetic denervation. *EuroIntervention*. 2022;18(8):e686-e694.
161. Taylor GW, Kay GN, Zheng X, Bishop S, Ideker RE. Pathological effects of extensive radiofrequency energy applications in the pulmonary veins in dogs. *Circulation*. 2000;101:1736-1742.
162. Bertog SC, Blessing E, Vaskelyte L, Hofmann I, Id D, Sievert H. Renal denervation: tips and tricks to perform a technically successful procedure. *EuroIntervention*. 2013;9(suppl R):R83-R88.
163. Bertog S, Fischel TA, Vega F, et al. Randomised, blinded and controlled comparative study of chemical and radiofrequency-based renal denervation in a porcine model. *EuroIntervention*. 2017;12:e1898-e1906.
164. Fischel TA, Vega F, Raju N, et al. Ethanol-mediated perivascular renal sympathetic denervation: preclinical validation of safety and efficacy in a porcine model. *EuroIntervention*. 2013;9:140-147.
165. Fischel TA, Ebner A, Gallo S, et al. Transcatheter alcohol-mediated perivascular renal denervation with the peregrine system: first-in-human experience. *JACC Cardiovasc Interv*. 2016;9:589-598.
166. Mahfoud F, Renkin J, Sievert H, et al. Alcohol-mediated renal denervation using the peregrine system infusion catheter for treatment of hypertension. *JACC Cardiovasc Interv*. 2020;13:471-484.
167. Schenk EA, el-Badawi A. Dual innervation of arteries and arterioles. A histochemical study. *Z Zellforsch Mikrosk Anat*. 1968;91:170-177.
168. Mancia G, Bombelli M, Corrao G, et al. Metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study: daily life blood pressure, cardiac damage, and prognosis. *Hypertension*. 2007;49:40-47.
169. Masuo K, Mikami H, Ogihara T, Tuck ML. Sympathetic nerve hyperactivity precedes hyperinsulinemia and blood pressure elevation in a young, non-obese Japanese population. *Am J Hypertens*. 1997;10:77-83.
170. Grassi G, Dell'Oro R, Facchini A, Quarti Trevano F, Bolla GB, Mancia G. Effect of central and peripheral body fat distribution on sympathetic and baroreflex function in obese normotensives. *J Hypertens*. 2004;22:2363-2369.
171. Huggett RJ, Scott EM, Gilbey SG, Stoker JB, Mackintosh AF, Mary DA. Impact of type 2 diabetes mellitus on sympathetic neural mechanisms in hypertension. *Circulation*. 2003;108:3097-3101.
172. Grassi G, Dell'Oro R, Quarti-Trevano F, et al. Neuroadrenergic and reflex abnormalities in patients with metabolic syndrome. *Diabetologia*. 2005;48:1359-1365.
173. Carnagaran R, Gregory C, Azzam O, et al. The role of sympatho-inhibition in combination treatment of obesity-related hypertension. *Curr Hypertens Rep*. 2017;19:99.
174. Scherrer U, Sartori C. Insulin as a vascular and sympathoexcitatory hormone: implications for blood pressure regulation, insulin sensitivity, and cardiovascular morbidity. *Circulation*. 1997;96:4104-4113.
175. Bardgett ME, McCarthy JJ, Stocker SD. Glutamatergic receptor activation in the rostral ventrolateral medulla mediates the sympathoexcitatory response to hyperinsulinemia. *Hypertension*. 2010;55:284-290.
176. Yakubu-Madus FE, Johnson WT, Zimmerman KM, Dananberg J, Steinberg MI. Metabolic and hemodynamic effects of moxonidine in the Zucker diabetic fatty rat model of type 2 diabetes. *Diabetes*. 1999;48:1093-1100.
177. Mahfoud F, Schlaich M, Kindermann I, et al. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation*. 2011;123:1940-1946.
178. Schlaich MP, Straznicki N, Grima M, et al. Renal denervation: a potential new treatment modality for polycystic ovary syndrome? *J Hypertens*. 2011;29:991-996.
179. Witkowski A, Prejbisz A, Florkacz E, et al. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. *Hypertension*. 2011;58:559-565.
180. Mancia G, Bousquet P, Elghozi JL, et al. The sympathetic nervous system and the metabolic syndrome. *J Hypertens*. 2007;25:909-920.
181. Koistinen HA, Zierath JR. Regulation of glucose transport in human skeletal muscle. *Ann Med*. 2002;34:410-418.
182. Verloop WL, Spiering W, Vink EE, et al. Denervation of the renal arteries in metabolic syndrome: the DREAMS-study. *Hypertension*. 2015;65:751-757.
183. Klein IH, Ligtnerberg G, Oey PL, Koomans HA, Blankestijn PJ. Sympathetic activity is increased in polycystic kidney disease and is associated with hypertension. *J Am Soc Nephrol*. 2001;12:2427-2433.
184. Grassi G, Quarti-Trevano F, Seravalle G, et al. Early sympathetic activation in the initial clinical stages of chronic renal failure. *Hypertension*. 2011;57:846-851.
185. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet*. 2010;376:1903-1909.
186. Hering D, Mahfoud F, Walton AS, et al. Renal denervation in moderate to severe CKD. *J Am Soc Nephrol*. 2012;23:1250-1257.
187. Schlaich MP, Bart B, Hering D, et al. Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease. *Int J Cardiol*. 2013;168:2214-2220.
188. Vonend O, Marsalek P, Russ H, Wulkow R, Oberhauser V, Rump LC. Moxonidine treatment of hypertensive patients with advanced renal failure. *J Hypertens*. 2003;21:1709-1717.
189. Campese VM, Kogosov E, Koss M. Renal afferent denervation prevents the progression of renal disease in the renal ablation model of chronic renal failure in the rat. *Am J Kidney Dis*. 1995;26:861-865.
190. Abramczyk P, Zwolińska A, Oficjański P, Przybylski J. Kidney denervation combined with elimination of adrenal-renal portal circulation prevents the development of hypertension in spontaneously hypertensive rats. *Clin Exp Pharmacol Physiol*. 1999;26:32-34.
191. Delacroix S, Chokka RG, Nelson AJ, et al. Renal sympathetic denervation increases renal blood volume per cardiac cycle: a serial magnetic resonance imaging study in resistant hypertension. *Int J Nephrol Renovasc Dis*. 2017;10:243-249.
192. Hering D, Mahfoud F, Walton AS, et al. Renal denervation in moderate to severe CKD. *J Am Soc Nephrol*. 2012;23:1250-1257.
193. Kiuchi MG, Graciano ML, Carneira MA, Kiuchi T, Chen S, Lugon JR. Long-term effects of renal sympathetic denervation on hypertensive patients with mild to moderate chronic kidney disease. *J Clin Hypertens (Greenwich)*. 2016;18:190-196.
194. Packer DL, Mark DB, Robb RA, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA*. 2019;321:1261-1274.



195. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. *Circ Res*. 2014;114:1500-1515.
196. Pokushalov E, Romanov A, Corbucci G, et al. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol*. 2012;60:1163-1170.
197. Kiuchi MG, Chen S, Hoye NA, Purerfellner H. Pulmonary vein isolation combined with spironolactone or renal sympathetic denervation in patients with chronic kidney disease, uncontrolled hypertension, paroxysmal atrial fibrillation, and a pacemaker. *J Interv Card Electrophysiol*. 2018;51:51-59.
198. Steinberg JS, Shabanov V, Ponomarev D, et al. Effect of renal denervation and catheter ablation vs catheter ablation alone on atrial fibrillation recurrence among patients with paroxysmal atrial fibrillation and hypertension: the ERADICATE-AF randomized clinical trial. *JAMA*. 2020;323:248-255.
199. Pranata R, Vania R, Raharjo SB. Efficacy and safety of renal denervation in addition to pulmonary vein isolation for atrial fibrillation and hypertension—systematic review and meta-analysis of randomized controlled trials. *J Arrhythm*. 2020;36:386-394.
200. Feyz L, Theuns DA, Bhagwandien R, et al. Atrial fibrillation reduction by renal sympathetic denervation: 12 months' results of the AFFORD study. *Clin Res Cardiol*. 2019;108:634-642.
201. Alexopoulos D, Yusuf S, Bostock J, Johnston JA, Sleight P, Yacoub MH. Ventricular arrhythmias in long term survivors of orthotopic and heterotopic cardiac transplantation. *Br Heart J*. 1988;59:648-652.
202. Berke DK, Graham AF, Schroeder JS, Harrison DC. Arrhythmias in the denervated transplanted human heart. *Circulation*. 1973;48:III112-III115.
203. Zhang B, Li X, Chen C, et al. Renal denervation effects on myocardial fibrosis and ventricular arrhythmias in rats with ischemic cardiomyopathy. *Cell Physiol Biochem*. 2018;46:2471-2479.
204. Linz D, Wirth K, Ukena C, et al. Renal denervation suppresses ventricular arrhythmias during acute ventricular ischemia in pigs. *Heart Rhythm*. 2013;10:1525-1530.
205. Armaganijan LV, Staico R, Moreira DA, et al. 6-month outcomes in patients with implantable cardioverter-defibrillators undergoing renal sympathetic denervation for the treatment of refractory ventricular arrhythmias. *JACC Cardiovasc Interv*. 2015;8:984-990.
206. Bradfield JS, Hayase J, Liu K, et al. Renal denervation as adjunctive therapy to cardiac sympathetic denervation for ablation refractory ventricular tachycardia. *Heart Rhythm*. 2020;17:220-227.
207. Evranos B, Canpolat U, Kocyigit D, Coteli C, Yorgun H, Aytemir K. Role of adjuvant renal sympathetic denervation in the treatment of ventricular arrhythmias. *Am J Cardiol*. 2016;118:1207-1210.
208. Jiang Z, Zhou X, Chen C, et al. Renal denervation for ventricular arrhythmia in patients with implantable cardioverter defibrillators. *Int Heart J*. 2018;59:328-332.
209. Kiuchi MG, Chen S, Paz LMR, Purerfellner H. Renal sympathetic denervation guided by renal nerve stimulation to treat ventricular arrhythmia in CKD patients with ICD. *Oncotarget*. 2017;8:37296-37307.
210. Ukena C, Mahfoud F, Ewen S, et al. Renal denervation for treatment of ventricular arrhythmias: data from an International Multicenter Registry. *Clin Res Cardiol*. 2016;105:873-879.
211. Bourke T, Vaseghi M, Michowitz Y, et al. Neuraxial modulation for refractory ventricular arrhythmias: value of thoracic epidural anesthesia and surgical left cardiac sympathetic denervation. *Circulation*. 2010;121:2255-2262.
212. Fudim M, Qadri YJ, Waldron NH, et al. Stellate ganglion blockade for the treatment of refractory ventricular arrhythmias. *JACC Clin Electrophysiol*. 2020;6:562-571.
213. Schwartz PJ, Priori SG, Cerrone M, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. *Circulation*. 2004;109:1826-1833.
214. Collura CA, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery. *Heart Rhythm*. 2009;6:752-759.
215. Vaseghi M, Lellouche N, Ritter H, et al. Mode and mechanisms of death after orthotopic heart transplantation. *Heart Rhythm*. 2009;6:503-509.
216. Pedrosa RP, Drager LF, Gonzaga CC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension*. 2011;58:811-817.
217. Somers VK, Mark AL, Zavala DC, Abboud FM. Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. *J Appl Physiol (1985)*. 1989;67:2101-2106.
218. Somers VK, Mark AL, Abboud FM. Sympathetic activation by hypoxia and hypercapnia—implications for sleep apnea. *Clin Exp Hypertens A*. 1988;10 (suppl 1):413-422.
219. Somers VK, Mark AL, Zavala DC, Abboud FM. Influence of ventilation and hypocapnia on sympathetic nerve responses to hypoxia in normal humans. *J Appl Physiol (1985)*. 1989;67:2095-2100.
220. Somers VK, Mark AL, Abboud FM. Potentiation of sympathetic nerve responses to hypoxia in borderline hypertensive subjects. *Hypertension*. 1988;11:608-612.
221. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96:1897-1904.
222. Warchol-Celinska E, Prejbisz A, Kadziela J, et al. Renal denervation in resistant hypertension and obstructive sleep apnea: randomized proof-of-concept phase II trial. *Hypertension*. 2018;72:381-390.
223. Hasking GJ, Esler MD, Jennings GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation*. 1986;73:615-621.
224. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med*. 1984;311:819-823.
225. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651-1658.
226. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med*. 1987;316:1429-1435.
227. Nozawa T, Igawa A, Fujii N, et al. Effects of long-term renal sympathetic denervation on heart failure after myocardial infarction in rats. *Heart Vessels*. 2002;16:51-56.
228. Davies JE, Manisty CH, Petraco R, et al. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. *Int J Cardiol*. 2013;162:189-192.
229. Gao JQ, Yang W, Liu ZJ. Percutaneous renal artery denervation in patients with chronic systolic heart failure: a randomized controlled trial. *Cardiol J*. 2019;26:503-510.
230. Spadaro AG, Bocchi EA, Souza GE, et al. Renal denervation in patients with heart failure secondary to Chagas' disease: a pilot randomized controlled trial. *Catheter Cardiovasc Interv*. 2019;94:644-650.
231. Zhou H, Li Y, Xu Y, et al. Mapping renal innervations by renal nerve stimulation and characterizations of blood pressure response patterns. *J Cardiovasc Transl Res*. 2022;15:29-37.
232. Liu H, Chen W, Lai Y, et al. Selective renal denervation guided by renal nerve stimulation in canine. *Hypertension*. 2019;74:536-545.

**ABDOMINAL AORTIC ANEURYSM, 407**

Introduction, 407

Diagnosis, 408

Indications for Revascularization, 408

Clinical Data, 409

Endovascular Repair, 411

Conclusions, 430

THORACIC ENDOVASCULAR AORTIC REPAIR, 430

Background, 430

Devices, 431

Indications for Thoracic Endovascular Aortic Repair, 431

Clinical Data for Thoracic Endovascular Aortic Repair, 431

Endovascular Technique for Thoracic Endovascular Aortic Repair, 434

Conclusions, 437

ABDOMINAL AORTIC ANEURYSM

Introduction

Abdominal aortic aneurysm (AAA) is defined as a 50% increase in the diameter of the aorta compared with a normal segment.¹ The average infrarenal aortic diameters for men and women are 1.5 cm and 1.7 cm, respectively. The universal standard for an infrarenal aneurysmal aorta is greater than 3.0 cm.²

Natural History

An AAA is usually asymptomatic and is most commonly discovered as an incidental finding on a radiologic examination. The prevalence of AAA increases with age, and the incidence in patients 45 to 54 years is 2.6% in men and 0.5% in women. In the older population (ages 75–84 years), the incidences of AAA are 19.8% in men and 5.2% in women. The overall prevalence of AAA varies from 5% to 7% in patients older than 65 years of age,³ and men are affected four to six times more often than women.³ A variety of cardiovascular and noncardiovascular comorbidities, such as hypertension, coronary artery disease, cerebrovascular disease, and malignancy, coexist with AAA.⁴ In patients with AAA, coronary artery disease and cerebrovascular disease are noted in 40% and 25%, respectively.⁵ Hypertension is present in more than half (55%) of patients with AAA, malignancy is noted in 23%, and claudication is noted in 28%.^{6,7} Approximately two-thirds (66%) of patients with AAA die from cardiovascular causes.⁸

Most aortic aneurysms increase at a rate of 0.2 to 0.3 cm/y when the size is smaller than 5.5 cm. However, when the aneurysm reaches 5 to 6 cm, there is a rapid increase of up to 3 cm/y.^{9,10} A rapid growth in an AAA is usually seen in smokers and women. The devastating sequelae of an enlarging AAA are catastrophic rupture and death. Ruptured AAA accounts for 1% of all deaths, and it is the 10th leading cause of death in patients older than 50 years of age.¹¹ Another clinical manifestation of AAA is distal embolization, resulting in acute limb ischemia, gangrene, blue toe syndrome, and limb loss.¹²

Risk Factors

The risk factors for AAA are similar to those for atherosclerosis: male gender, age older than 65 years, a history of ever smoking (>100 cigarettes in a person's lifetime), hypertension, hypercholesterolemia, and genetic predisposition.^{13–15} Patients with type 2 diabetes have a lower risk of developing AAA than people without diabetes. People with diabetes who develop AAA tend to have slower growth and a lower risk of rupture than people without diabetes. The protective effect is postulated to be from hyperglycemia-induced aortic wall thickening and the protective effect of metformin.¹⁶ One of the potential risk factors is a family history of AAA and surgical interventions for AAA in a family member.^{16,17,18} Five percent of patients with AAA have associated thoracic aneurysms, and approximately 15% have associated femoral or popliteal aneurysms.^{19,20}

Inflammatory aneurysms are a unique subset (5%) of AAA and usually present with vague flank pain, abdominal discomfort, and fever. Computed tomography (CT) or magnetic resonance imaging (MRI) usually demonstrates concentric thickening around the abdominal wall. The inflammatory process in the retroperitoneum is extensive and often involves the inferior vena cava, ureters, renal vein, and duodenum. When such an AAA reaches 5.5 cm, the endovascular approach may be optimal.²¹

A minority of AAAs are associated with a nonatherosclerotic degenerative connective tissue disease, such as Ehlers-Danlos syndrome, Marfan syndrome, and Loeys-Dietz syndrome.²² Mycotic aneurysms are rare but can cause pseudoaneurysms, and the most common causes are *Salmonella* and *Staphylococcal aureus*. Surgical options include resection and extraanatomic bypass or aorta bifemoral bypass using the deep femoral veins. Patients with mycotic aneurysms commonly have comorbidities; therefore, the surgical approach may be prohibitive. Endovascular aneurysm repair (EVAR) for treatment of abdominal mycotic aneurysms may be a short-term solution to avoid catastrophic rupture.^{22,23} Rare complications of AAA are aortoenteric fistula and iliac or vena cava compression presenting as a venoocclusive or thromboembolic event.



There are case reports of successful exclusion of aortoenteric fistulae using an endograft.^{24,25} An example of aortoenteric fistula treated with an aortic stent graft and esophageal covered stent in a patient with gastrointestinal (GI) malignancy is shown in Case 1.

Laplace Law

Laplace law indicates that wall tension of a symmetric shape is directly proportional to the intraluminal pressure and inversely proportional to the wall thickness. However, in reality, AAAs are not symmetrical in shape and have variations in wall thickness and strength.

Predictors of Rupture

The maximum AAA diameter is the most extensively accepted single parameter that predicts the risk of rupture.^{9,10} The risk of rupture increases when the AAA size is greater than 5.5 cm in men and women. The expansion rate is also an important determinant of risk of rupture.^{4,26} Rapidly enlarging AAAs, defined as a growth of 0.5 cm every 6 months, are also considered to be at high risk for rupture.²⁷ Continued smoking and lifting heavy weights can cause a rupture in patients with aneurysms.³⁰ Intraluminal thrombus that is both inflammatory and thrombogenic can create cellular destruction from oxidative stress, apoptosis of vascular smooth muscle cells, and proteolysis of the extracellular matrix.^{28,29,30} The increased intraluminal thrombus reduces peak and mean wall stress and is associated with AAA rupture despite its small diameter.^{31,32}

Diagnosis

Physical Examination

Despite the novelty and importance of a physical examination, the only reliable finding is a widened palpable or pulsatile aorta above the umbilicus. Only 30% of these asymptomatic AAAs are detected on routine physical examination as a pulsatile abdominal mass.³³ Auscultation of the aneurysm is useful because the presence of a bruit may indicate associated aortic or mesenteric artery occlusive disease. Occasionally, a machinery murmur over the aneurysm may indicate an aortocaval fistula. The physical examination is dependent on the clinician's experience and the patient's body habitus. A large aneurysm in a thin individual is detected easily, but the accuracy of physical examination is reduced by an obese body habitus. The overall sensitivity is approximately 29%, but it can reach 96% in patients with an aneurysm that is 5.0 cm or larger.^{33,34} The absence of a widened or palpable aorta does not exclude the presence of an AAA. Concomitant aneurysms, such as femoral and popliteal aneurysms, can be more easily diagnosed yet continue to be underdiagnosed. Other physical examination findings can be distal arterial embolization, blue toe syndrome (or livedo reticularis), and diminished distal pulses.

Abdominal Ultrasonography

This is a safe, cost-effective, and simple test of choice for screening patients with AAA. The sensitivity and specificity of ultrasonography, when performed by trained personnel, are close to 96% and 100%, respectively, for

detection of infrarenal AAA.³⁴ Ultrasonography can serve as an excellent tool for the diagnosis and follow-up of AAA. Poor imaging quality because of patient body habitus and variations in interpretations are a few of the notable limitations.³⁵

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) is a noninvasive test used to diagnose and evaluate the size of an AAA; however, MRA cannot usually be performed on patients with metallic implants, such as pacemakers.³⁶

Computed Tomography

Computed tomography scans can not only confirm the precise size, but they can also delineate thrombus, occlusion, or stenosis.^{37,38} CT scanning plays a pivotal role in planning EVAR versus open repair and follow-up for shrinkage of size and endoleaks. The details of use of CT scan in preplanning an EVAR are described later in this chapter.

Indications for Revascularization

Symptomatic Patients

When an AAA becomes symptomatic, it can be categorized into the following:

1. Impending rupture
2. Embolic or thrombotic complications
3. Mass effect

Patients with symptomatic AAA usually present with abdominal pain, low back pain, and flank pain. A sudden onset of back pain or abdominal pain, hypotension, and a palpable abdominal mass are the classic triad of symptoms for a ruptured AAA. However, a clinical diagnosis for ruptured AAA requires a high index of suspicion and misdiagnosis that includes renal colic, perforated viscus, abdominal wall hernia, diverticulitis, and ischemic bowel.^{38,39}

Thromboembolic symptoms from AAA can cause acute limb ischemia, gangrene, and limb loss. Baxter et al.⁴⁰ identified 15 patients, among a review of 302 patients undergoing open AAA repair, to have distal embolization as the first manifestation. Among these patients, only 2 had an AAA size larger than 5 cm, which is suggestive of the potentially dangerous nature of small AAAs that are more likely to present with thromboembolic symptoms (Figure 23.1). Large AAAs may cause vague symptoms, such as back pain, early satiety, ureteral compression, lower GI bleed from aortoenteric fistula, and venous thrombosis due to ilio caval compression.

Asymptomatic Aneurysms

Patients with AAA are generally asymptomatic and are found during incidental radiological tests, such as radiography, ultrasonography, CT, MRI, and positron emission tomography (PET). The maximum diameter of the AAA is the best indicator of rupture.⁴¹ The generally accepted indications are that men and women with an AAA larger than 5.0 to 5.5 cm require revascularization because of an increased risk of rupture.^{42,43} Rapidly growing aneurysms, defined by a growth rate greater than 0.5 cm in 6 months or 1.0 cm in 1 year, also need revascularization.⁴⁴ Factors that should be considered include estimated risk of rup-

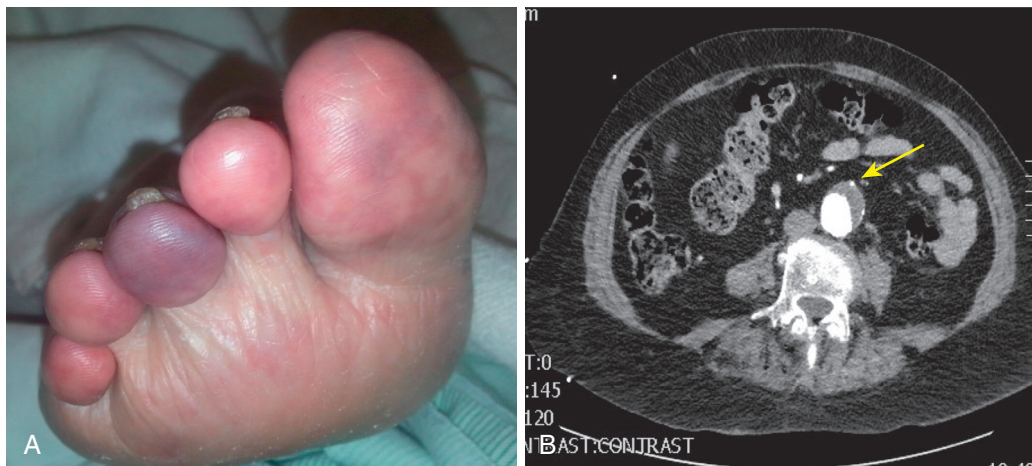


FIGURE 23.1 A 76-year-old patient with blue toe syndrome (A) from a 3.5-cm abdominal aortic aneurysm (B, arrow).

ture under observation, the operative risk involved, the life expectancy of the patient, and the patient's personal preferences.

Clinical Data

The first EVAR was performed by Drs. Parody, Palmaz, and Barone on September 7, 1990; by 1991, five more patients were treated with EVAR.⁴⁵ A Dacron tube prosthesis was inserted via the transfemoral approach, and the fixation was by balloon expandable stents. Subsequently, the non-stented bifurcated or straight devices were described by White et al.⁴⁶ White and colleagues published the data in 25 patients with the use of a novel graft attachment device. Successful EVAR was achieved with low morbidity and mortality in patients who met the selection criteria.

Ivancev et al.⁴⁷ performed an endoluminal exclusion of AAA using an aortomonoiliac stent graft. A total of 45 patients underwent exclusion of AAA using the unilimb device, which was deployed with the "Lancey-Mamosystem." Open surgical conversion was performed in 6 patients because of the short length of the endograft device. Several complications were noted, such as 2 patients with inadvertent renal artery occlusions, 6 patients with iliac artery dissections, 7 patients with kinked grafts, and 3 patients with perioccluder leaks. A total of 5 patients died in the perioperative period, and 5 more patients had significant migrations. The study proved the feasibility of graft use, but complications from a learning curve were clearly noted. This study also demonstrated the need for adherence to a strict inclusion protocol to improve mortality and reduce complications.

By 1997, six endovascular grafts were commercially available. The individual treatment strategies for each device and specific inclusion criteria were described.⁴⁸ The initial treatment of ruptured AAA with EVAR was reported by Dr. Yusuf et al.⁴⁹

Initial Comparisons of Open Surgical Repair Versus Endovascular Abdominal Aortic Aneurysm Repair

The widespread use of EVAR to treat AAA followed the Food and Drug Administration (FDA) approval of second-generation abdominal aortic endograft in 1999.

The early EVAR outcomes noted in nonrandomized trials, registries, and single-center trials demonstrated lower rates of mortality and morbidity. A comparison of endoluminal versus open repair in the treatment of AAAs was analyzed in 303 patients.⁵⁰ Open repair was performed in 195 patients and endovascular repair in 108 patients. The perioperative mortality rates were 5.6% each in the open repair group and the endovascular group. The advantages of endovascular repair were lower blood loss, shorter intensive care unit (ICU) stay, and reduced neurologic complications. However, the Achilles heel of EVAR continued to be late complications such as endoleak and migration.

After 15 years of initial EVAR, by 2006 in the United States, 21,725 endovascular exclusion of AAA procedures were performed, and thus EVAR numbers exceeded the number of open surgical AAA revascularization.⁵¹ The recent developments in catheter-based endovascular techniques led to a substantial increase in the proportion of AAAs managed electively with EVAR. As of 2012, more than 70% of all infrarenal AAA was being treated with EVAR in the United States.⁵²

Randomized Controlled Trials of Endovascular Aneurysm Repair Versus Open Surgical Repair

The landmark trials that demonstrated the safety, efficacy, and long-term results of EVAR versus open surgical repair for AAA were the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, Endovascular Aneurysm Repair 1 (EVAR I), Endovascular Aneurysm Repair 2 (EVAR 2), and OVER (Open Versus Endovascular Repair) trial (Table 23.1).

Dream

The DREAM trial was first published in 2004, and the long-term results were published in 2010. DREAM was a randomized, controlled, multicenter trial (24 centers in Netherlands and 4 centers in Belgium) comparing EVAR with open repair in 351 patients with AAAs greater than 5 cm who were suitable for both techniques. The primary endpoint was death from any cause and intervention. A total of 173 patients were randomly assigned to EVAR and 178 patients to open repair. There was no statistically significant difference found in the primary endpoint at

TABLE 23.1 Summary of Randomized Control Trials Comparing Outcomes of Open Versus Endovascular Repair for Abdominal Aortic Aneurysm

OUTCOMES	DREAM		EVAR 1		OVER	
	OPEN REPAIR	ENDOVASCULAR REPAIR	OPEN REPAIR	ENDOVASCULAR REPAIR	OPEN REPAIR	ENDOVASCULAR REPAIR
30-day mortality rate (%)	4.6	1.2	4.3	1.8	3	0.5
Long-term mortality rate	30.1% at 6 y	31.1% at 6 y	22.3% at 4 y	23.1% at 4 y	9.8% at 2 y	7.0% at 2 y

DREAM, Dutch Randomized Endovascular Aneurysm Management; EVAR, Endovascular aneurysm repair; OVER, Open Versus Endovascular Repair.

30 days between the surgical group and EVAR (9.8% vs 4.7%; $P = .10$). At 6 years, the cumulative survival rates were 68.9% for endovascular repair and 69.9% for surgical repair (95% confidence interval [CI], -8.8 to 10.8 ; $P = .97$). The rate of secondary intervention at 6 years in the EVAR group was 29.6% and open repair 18.1% ($P = .03$). The EVAR did have a lower procedural blood loss, systemic complications, need for mechanical ventilations, and shorter ICU and hospital stay.

The updated results of the DREAM trial with up to 15 years of follow-up were recently published. At 12 years, the cumulative survival rates were 42.2% for open repair and 38.5% for EVAR, a 3.7% difference (95% CI, -6.7 to 4.1 ; $P = .48$). The cumulative rates of freedom from reintervention were 78.9% for open repair and 62.2% for EVAR (95% CI, 5.8 – 27.6 ; $P = .01$). There were no differences in causes of death. The primary cause of death was malignancy and cardiovascular disease.⁵³

EVAR 1

In this trial, 1252 patients from 37 hospitals in the United Kingdom between 1999 and 2004 were enrolled.⁵⁴ All patients had AAAs larger than 5.5 cm and were considered to be acceptable candidates for either open repair or EVAR. A total of 626 patients were enrolled into each group, and they were followed until 2009 for mortality rates, complications from graft, reinterventions, and resource use. The 30-day mortality rate for the endovascular group was 1.8% versus 4.3% in the open repair group ($P = .02$). Despite the early benefit with aneurysm-related mortality rate in the EVAR group, by the end of the study, there was no difference in mortality from any cause between the two groups ($P = .73$). Similar to the DREAM trial, EVAR 1 also showed higher rates of graft-related complications and reinterventions with EVAR and higher costs.

At a mean of 12.7 years (standard deviation, 1.5; full 15.8 years) of follow-up, 9.3 deaths per 100 person-years occurred in the EVAR group, and 8.9 deaths per 100 person-years occurred in the open group (adjusted hazard ratio [HR], 1.11; 95% CI, 0.97–1.27; $P = .14$). At 8 years, the open repair had significantly lower mortality (adjusted HR, 1.25; 95% CI, 1.00–1.56; $P = .048$ for total mortality and 5.82, 1.64–20.65, $P = .0064$ for aneurysm-related mortality). At 8 years, the EVAR group showed an increase in aneurysm-related mortality rate mainly caused by aneurysm sac rupture (13 deaths [7%] in EVAR vs 2[1%] in open repair). Increased malignancy-related deaths were observed in the EVAR group.⁵⁴

Evar 2

The EVAR 1 investigators randomized 338 patients with AAAs larger than 5.5 cm unfit for open repair to endovascular

repair ($n = 166$) versus no intervention ($n = 177$).⁵⁵ The 30-day operative mortality rate in the endovascular group was 9%. The rupture rate in the no intervention group was 9 per 100 person years. At 4 years of follow-up, there was no difference in all-cause mortality ($P = .25$). The aneurysm-related mortality was lower in the EVAR group (adjusted ratio, 0.53; $P = .02$). However, EVAR was associated with higher hospital costs and no benefit in terms of patient quality of life compared with the noninterventional group. The complication rates were higher in the endovascular group—48% versus 18% in the noninterventional group ($P < .0001$).

Over

The OVER trial was conducted at 42 Veteran Affairs medical centers in the United States.⁵⁶ OVER was a multicenter, randomized trial that enrolled a total 881 patients with AAA who were eligible for open surgical repair or EVAR. The enrolled patients had an AAA maximum diameter larger than 5.0 cm, iliac artery aneurysm larger than 3.0 cm, or AAA larger than 4.5 cm and had rapid AAA enlargement (>0.5 cm in 6 months) or secular aneurysms. A total of 437 patients were randomized to open repair and 444 patients to EVAR. The primary outcomes measured were procedure failure, secondary procedures, length of stay, quality of life, erectile dysfunction, mortality, and major morbidity. The 30-day perioperative mortality rate was lower for EVAR compared with open repair (0.5% vs 3.0%; $P = .04$). However, this early EVAR benefit was lost at 2 years; the perioperative mortality rates for open and EVAR were 9.8% versus 7.0% ($P = .13$). The EVAR group had reduced procedure time, transfusion requirement, blood loss, and hospital and intensive care stay. There were no differences in procedural failure, secondary procedures, quality of life, and erectile dysfunction incidence between the two groups.

At 4 years of follow-up, the overall survival rate was higher in the EVAR group compared with open repair. A total of 302 patients (68%) in the EVAR group and 306 patients (70%) in the open repair group died (HR, 0.96; 95% CI, 0.82–1.13). The follow-up period from 4 to 8 years showed that the overall survival rate was higher with the open group than the EVAR group. After 8 years of follow-up, the survival rate was higher in the EVAR group (HR for death, 0.94; 95% CI, 0.74–1.18). The EVAR group had 12 aneurysm-related deaths (2.7%) versus 16 deaths (3.7%) in the open group (between-group difference, -1.0 percentage point; 95% CI, -3.3 to 1.4); the majority of deaths were in the perioperative period. In the EVAR group, aneurysm rupture occurred in 7 patients (1.6%), and rupture of thoracic aneurysm occurred in 1 patient (0.2%) in the open repair group (between-group difference,

TABLE 23.2 Various Characteristics That Should Be Evaluated on the Preoperative Computed Tomography Angiography of an Abdominal Aortic Aneurysm

LOCATION	PARAMETER	MEASUREMENTS	DEVICE INSTRUCTIONS FOR USE
Aortic neck	Diameter	Measure at the level of lowest renal artery and 15 mm caudal a. 10 mm for Medtronic Endurant device b. 7 mm for Trivascular Ovation device	Should be 16–32 mm
	Length	Distance from lowest renal artery to the origin of aneurysm	>15 mm for most devices a. 10 mm for Medtronic Endurant device b. 7 mm for Ovation Trivascular device
	Angulation	Between the central line of aorta and aneurysm	<60 degrees a. <90 degrees for Lombard Aorfix device
	Thrombus	Should be <25% of vessel circumference	
	Calcification	Extensive or circumferential predicts problems with good seal	
	Taper	Look for reverse taper (>4-mm diameter increase over 10-mm aortic length)	Increases chances of proximal type I endoleak
Distal aortic bifurcation		Look for narrowing that may preclude the accommodation of two limbs of the graft except for Endologix Powerlink device	
External iliac artery		Should be able to accommodate a 14- to 20-Fr sheath depending on the type of device A minimum of 6 mm EIA is recommended for the low-profile device	
Hypogastric artery		For patency, length between CIA and hypogastric origin and aneurysms	
Femoral arteries		For anterior versus posterior calcium, plaque, patency, and aneurysmal dilation	

CIA, Common iliac artery; EIA, external iliac artery.

1.3 percentage points; 95% CI, 0.1–2.6). Death from chronic lung disease was 50% more common in the open group, and more secondary procedures were performed in the EVAR group. The long-term results of OVER are inconsistent with findings of long-term follow-up of EVAR 1 and DREAM (both European) clinical trials. The long-term overall survival rates were similar in EVAR and open repair.

A 2019 meta-analysis of seven randomized controlled trials of 2983 patients who underwent EVAR versus open repair was analyzed. The meta-analysis found significantly lower odds of hospital mortality at 30 days (Risk Difference, 0.03; 95% CI -0.04 to -0.02) in the EVAR group (odds ratio, 0.36; 95% CI, 0.20–0.66). During long-term follow-up (>8 years), the aneurysm-related mortality rate was higher with EVAR (HR, 5.12; 95% CI, 1.59–16.44). The risk of secondary intervention, aneurysm rupture, and death caused by rupture was higher with EVAR.⁵⁷

Endovascular Repair

Preoperative Imaging

Multiple modalities such as CT angiogram, MRA, intravascular ultrasonography (IVUS), and angiography are available to image AAAs. A contrasted CT scan using the thin slices (0.9–3.0 mm) is the imaging modality of choice for preoperative evaluation of AAA before EVAR. In patients with significant renal insufficiency, CT without contrast and MRA without gadolinium may be used. Such alternative techniques may miss important anatomical information such as: laminated thrombus, patent inferior mesenteric artery (IMA), and severe iliofemoral occlusive disease.^{58,59} Besides the axial cuts, a review of

sagittal, coronal, and three-dimensional (3D) reconstructions is necessary to fully understand the aneurysm anatomy, including its angulation (Table 23.2). IVUS can be used to size the aortic and iliac artery seal zones, and evaluate potential eccentric thrombus in the aortic neck and the external iliac artery for occlusive disease (Figures 23.2 and 23.3).

Anesthesia

All patients scheduled for elective EVAR should undergo appropriate preoperative risk stratification according to American College of Cardiology/American Heart Association guidelines. Patients who are considered inoperable for open surgical repair of AAA carry a risk of 18% to 43% perioperative cardiovascular events if primary conversion of EVAR to surgical open repair becomes necessary.⁶⁰ Initially, the majority of patients received general anesthesia (GA) for EVAR. The smaller sheath size and closure devices have enabled patients to undergo EVAR with monitored anesthesia care (MAC).^{61,62} The evolving role of local, regional, MAC, and spinal anesthesia are being compared with standard GA to perform EVAR. Armstrong and colleagues studied 6009 patients who underwent elective EVAR. GA was used in 4868 cases, spinal anesthesia in 419, epidural in 331, and local or MAC in 391. The overall mortality rate was 1.1%. GA was associated with increased pulmonary morbidity compared with spinal or MAC. GA was associated with a 10% increase in length of stay for versus spinal and a 20% increase for GA versus MAC.⁶³ EVAR operators should coordinate and plan the procedure with the anesthesia for procedure safety and reduce complications.

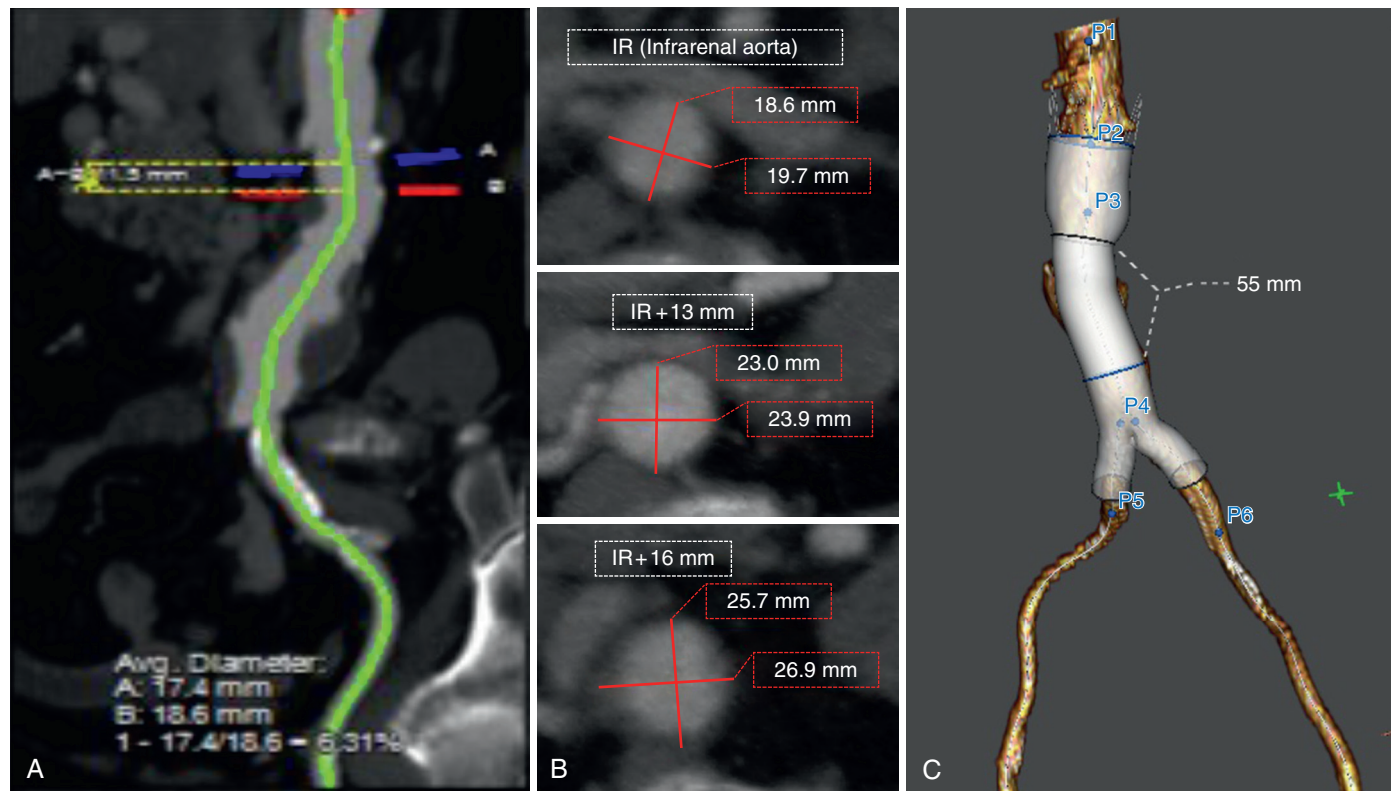


FIGURE 23.2 Computed tomography scan for pre-endovascular aneurysm repair (EVAR) planning. **A**, Center line measurements for infrarenal neck length and diameter. **B**, Infrarenal neck measured at 1, 13, and 16 mm below the lowest renal artery. **C**, Three-dimensional image reconstruction of EVAR graft superimposed on the abdominal aortic aneurysm.

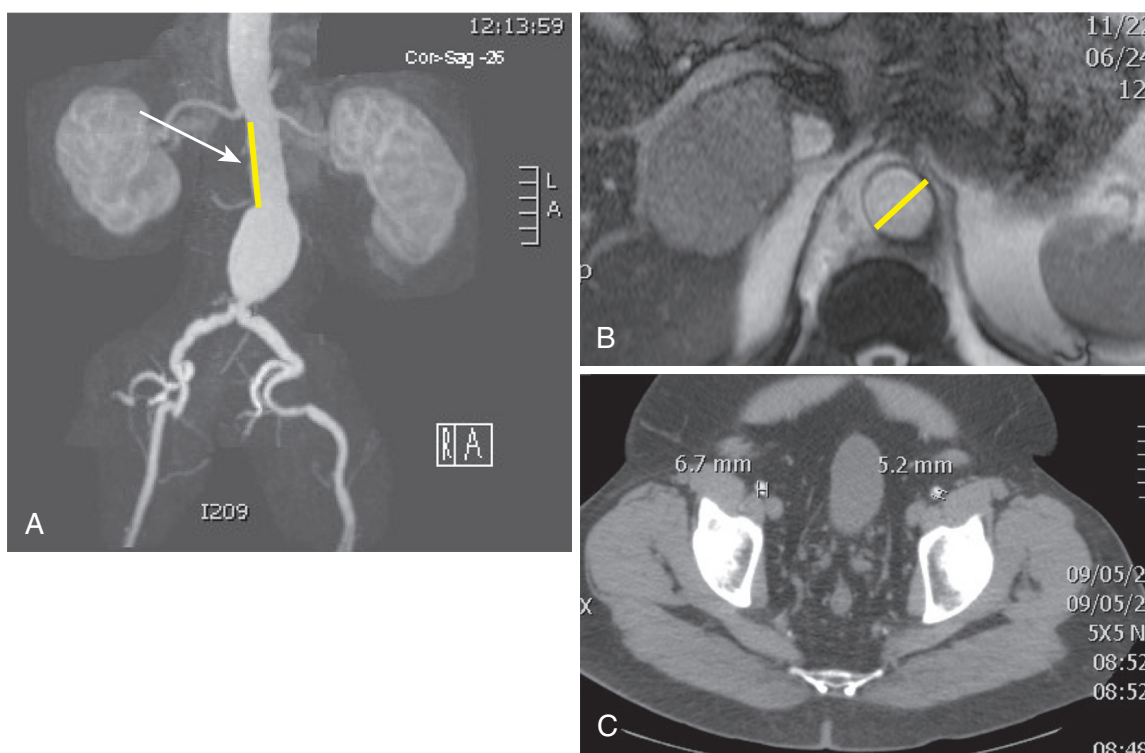


FIGURE 23.3 Magnetic resonance angiography for pre-endovascular aneurysm repair planning. **A**, Neck length (arrow and yellow line). **B**, Diameter (yellow line). **C**, External iliac diameter.

Strategic Planning and Multispecialty Team

A careful and well-thought-out strategic plan of EVAR is essential for optimal outcomes. The planning should include a physical examination and detailed history and a thorough explanation of the natural history of AAA to the patient and family. The multispecialty (vascular surgeon, cardiologist, radiologist) discussion should include all treatment options for AAA revascularization and risk-to-benefit ratio and alternatives of EVAR. Each EVAR case should be preferably planned with a vascular surgeon and anesthesiologist in a team-based approach. Recent advances in CT software technology include the availability of 3D measurements to assist in intraoperative navigation techniques.⁶⁴ All high-risk patients should have risk factor reduction by appropriate treatment with aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins before EVAR. Baseline pulmonary functions test and laboratory studies such as blood urea nitrogen, creatinine, hemoglobin levels, and prothrombin time should be known before surgery. Anticoagulants such as warfarin or newer ones should be held in advance and, if needed, bridged with heparin. A type and screen of blood type rather than type and cross can reduce the number of transfusions.⁶⁵ All the devices and auxiliary equipment such as snares, covered stents, and a Palmaz Genesis peripheral stent (Cordis,) should be available before the start of the case.

Endovascular aneurysm repair is performed by various specialists who have proficiency in the procedure and follow-up. The multispecialty team usually should include vascular surgery, cardiology or radiology, and anesthesia.

Despite the ability of a nonvascular surgery physician to perform EVAR, it is highly recommended to have a team approach with vascular surgery. Such a team approach plays a vital role in endovascular management of ruptured AAA.⁶⁶ Acute complications such as vessel rupture, distal embolization, requirement for a surgical cutdown for vessel access and repair, or emergent conversion to open repair all need vascular surgery expertise.⁶⁷

Anatomic Considerations

Anatomic considerations that are important for AAA suitability for EVAR are as follows:

- Proximal and distal attachment site
- Diameter and characteristics of access vessels
- Percutaneous access for EVAR
- Aortoiliac artery side branches with potential for exclusion during EVAR: hypogastric artery, accessory or anomalous origin of renal artery, and patent IMA

Proximal and Distal Attachment Sites

One of the most important anatomic factors that predicts the suitability for EVAR is the character of aortic neck. Important measurements and characteristics include length, diameter, angulations, presence of thrombus, reverse taper, and calcification. The majority of the endovascular grafts have prespecified instructions for use (IFU)—the infrarenal neck length should be at least 10 mm in length and less than 32 mm in diameter with infrarenal angulations less than 90 degrees (Figures 23.4 and 23.5).⁶⁸ Newer endovascular stent grafts' role in treating short neck AAA has

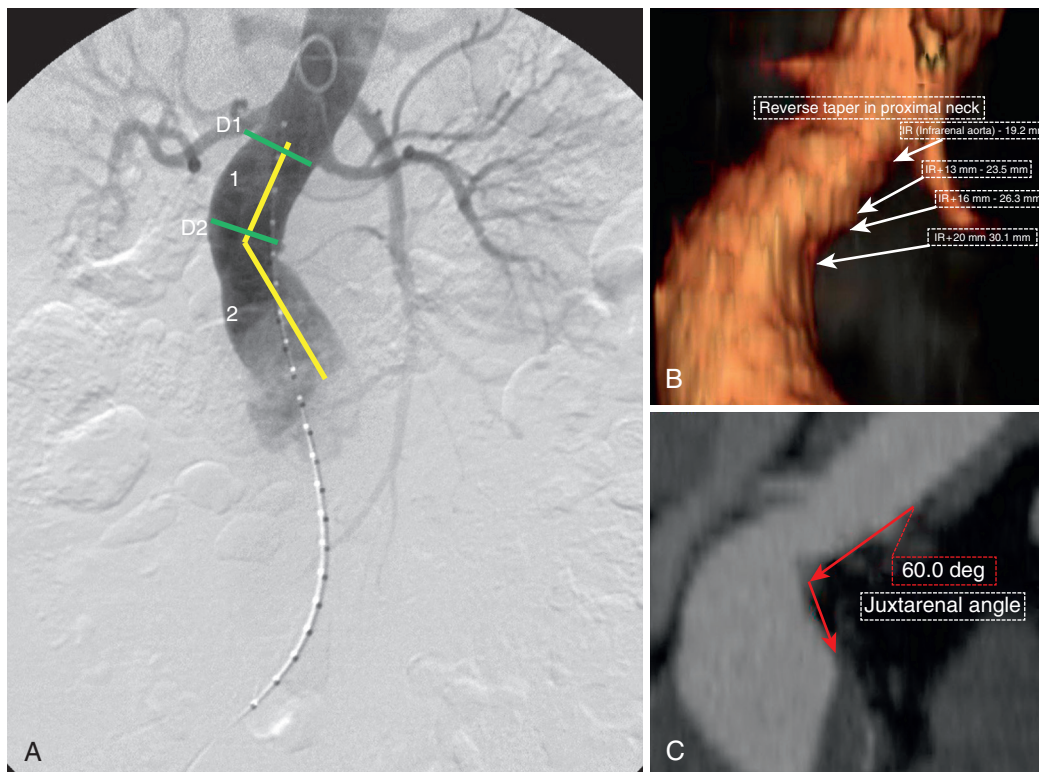


FIGURE 23.4 Case example of aortic neck characteristics that are ideal for endovascular aneurysm repair (EVAR). **A**, 1, Length of the aneurysmal neck; D1, diameter of the proximal neck; D2, diameter of the distal neck; 2, angulation of the neck. **B** and **C**, Reverse taper of the aortic neck.

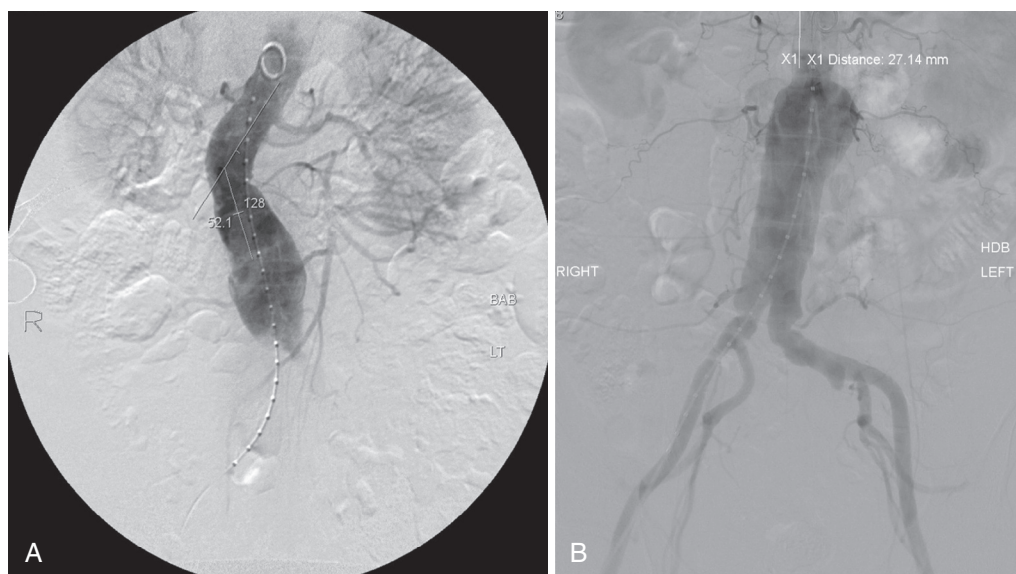


FIGURE 23.5 Angiographic confirmation of aortic neck measurements. **A**, Infrarenal neck angulation. **B**, Infrarenal neck length.

shown mixed results. AAAs larger than 5.0 cm with short necks smaller than 7 mm versus larger than 7 mm underwent an Ovation stent graft device (Endologix), and at 5 years, there were no differences in type Ia endoleak, reintervention, and aneurysm-related death. However, a short neck was independently associated with a twofold increase in the risk of all-cause mortality at 5 years.⁶⁹

Aortic Neck: Diameter, Length, Angulation, Taper, Reverse Taper, and Thrombus

The aortic neck is the portion of the healthy aortic tissue between the top of the aneurysm sac and the lowest renal artery (vessel diameter is 10% greater than the aorta at the lowest renal artery). Aortic neck diameters that can be treated can range from 18 to 32 mm. Most measurements are based on the CT scan outer wall to outer wall except for Gore (W.L. Gore and Associates), which measures inner to inner wall. The two important dimensions of the infrarenal neck of the AAA are measured as D1 and D2. D1 is the first image of the infrarenal aorta measured outer to outer wall in the short axis. D2 is the diameter below D1 at 10 mm or 15 mm distal based the graft. The length of the aortic neck is determined by counting the number of images from lower renal artery to the start of the aneurysm based on the CT scan slices at the time of imaging (0.9–5.0 mm).

The distal attachment site is equally important to ensure adequate seal and prevent endoleak (discussed later). The distal landing zone is preferable in the common iliac artery and allows perfusion of the hypogastric artery. In patients with common iliac artery (CIA) aneurysms, the endovascular approach can be performed with low morbidity, blood loss, hospital stay, and short-term mortality.⁷⁰ The midterm durability and survival from endovascular approach offers the advantage of first-line treatment option for patients with iliac artery aneurysms (Figure 23.6).^{71,72} The diameter of the CIA and morphology such as calcification, thrombus, and stenosis should be evaluated. CIA diameters up to 25 mm can be treated with endograft using a

flared 28-mm limb available with Endurant stent graft system (Medtronic).

The two main issues of obliteration of hypogastric arteries are pelvic ischemia and type II endoleak (explained later). A large series of EVAR patients who underwent hypogastric embolization had persistent buttock claudication in 12% of unilateral and 11% of bilateral hypogastric artery interruptions. Erectile dysfunction occurred in 9% of unilateral and 13% of bilateral hypogastric occlusions.⁷³ The dreaded complication of ischemic colitis develops in fewer than 2% of EVAR cases.⁷⁴ The risk for colon necrosis increases in EVAR patients who have an occlusive disease of all three mesenteric vessels or if previous colon surgery has interrupted the mesenteric collateral pathways. Colon ischemia is more likely to result from atheroembolism to the pelvic circulation rather than hypogastric artery occlusion.⁷⁵

The characteristics of the common iliac artery can determine the following options that are available to manage the distal landing zone during EVAR (Figure 23.7).

1. If the internal iliac artery is not aneurysmal, coil embolization of the internal iliac artery is performed at its origin to reduce the postprocedure rates of buttock claudication.⁷⁶ The patency of branches of internal iliac artery may help in reducing buttock claudication postprocedure. The limb can be further extended across the embolized hypogastric artery into the external iliac artery (EIA) to obtain adequate seal.
2. If flow to the internal iliac artery has to be preserved, then a surgical bypass from internal iliac artery to the external iliac artery can be performed. This hybrid technique has demonstrated good mid- and long-term patency.⁷⁷ However, the operative times, length of hospital stay, and blood loss are increased.

If the hypogastric artery needs to be preserved, a double-barrel stenting can preserve the flow to the internal iliac artery and obtain adequate seal at the common iliac artery.^{78,79} In this technique, one covered stent is placed from the CIA into the hypogastric artery, and a

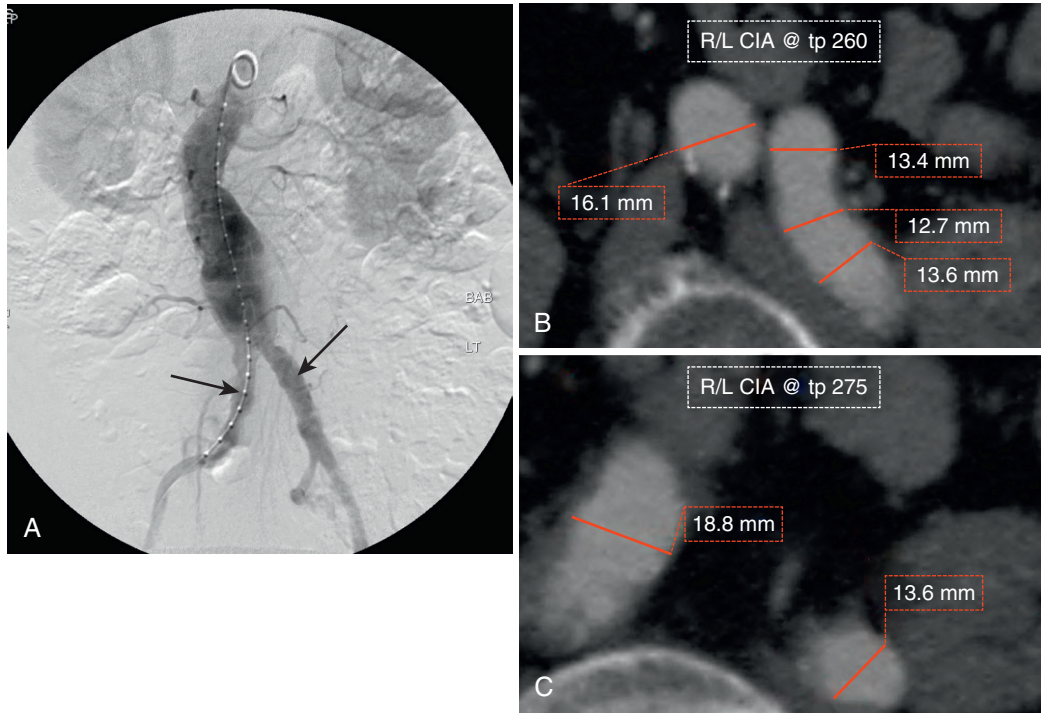


FIGURE 23.6 Common iliac artery (CIA) with a good landing zone in a patient evaluated for endovascular aneurysm repair. **A**, Angiography. **B** and **C**, Computed tomography scan. *L*, Left; *R*, right; *tp*, is tissue property filter that a radiology reports.

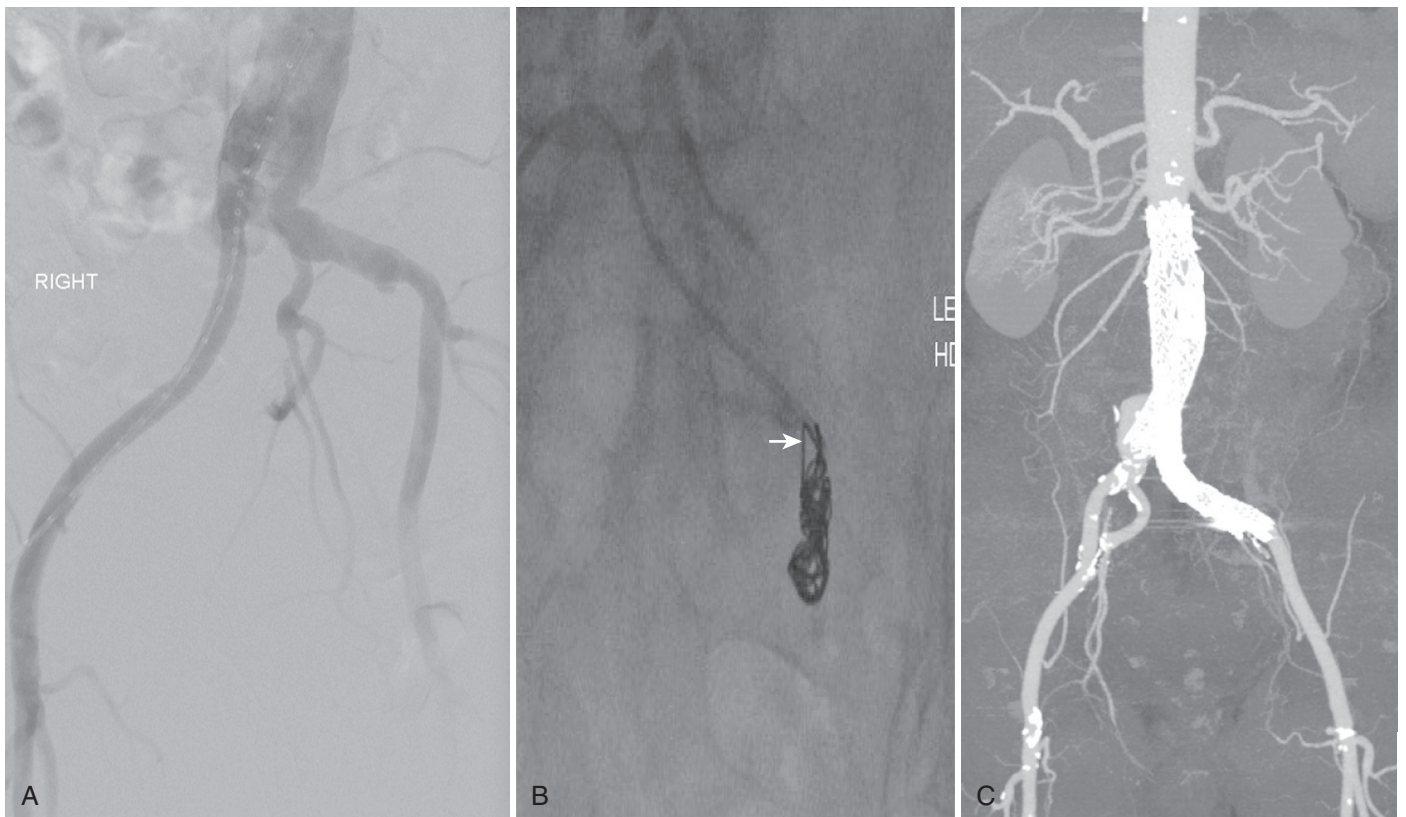


FIGURE 23.7 **A**, Pre-endovascular aneurysm repair (EVAR) angiogram to treat a 3.2-cm common iliac artery aneurysm and abdominal aortic aneurysm. **B**, The internal iliac artery is occluded at the origin (arrow) by coil embolization. **C**, Computed tomography follow-up shows limb of the EVAR graft extended into the external iliac artery.



FIGURE 23.8 A case of sandwich technique during endovascular aneurysm repair (EVAR) to maintain hypogastric artery patency. **A**, The left hypogastric artery shows severe ostial stenosis. **B**, Simultaneous stenting of left hypogastric artery and left external iliac artery (EIA). **C**, Final angiogram to show preservation of the left hypogastric artery and the left EIA.

simultaneous limb of the EVAR graft extends from the CIA to the EIA (Figure 23.8). A prospective multicenter US clinical trial using Gore Excluder iliac branch endoprosthesis (IBE) studied outcomes of treatment of iliac and aortoiliac aneurysms. At 6 months, the IBE patency was 95%, with no type I or type 3 endoleaks, and freedom from reintervention was 98.4%. There was no ipsilateral new onset buttock claudication. In the same study, patients with bilateral iliac artery aneurysms who underwent the sacrifice of one hypogastric artery showed a 28% incidence of buttock claudication on the side of the sacrificed hypogastric artery.^{80,81}

3. If the common iliac artery is occluded, then a uni-aortic limb placement with femoral-femoral bypass is performed.⁸² A contralateral placement of flexible covered stent from external iliac artery to internal iliac artery allows retrograde perfusion.⁸³

Access Arteries

The bilateral common femoral artery (CFA) is the most common access site for insertion of the delivery sheath or the device. The majority of the devices need a prespecified sheath through which the device can be inserted. The access vessels are evaluated for atherosclerosis, stenosis, calcification, and vessel diameters (Figure 23.9). The CFA should be accessed for vessel length, depth of the artery from skin surface, and diameter. The calcification of the

CFA is a critical determinant of the technical success and outcomes of EVAR.⁸⁴

Calcification, atherosclerosis, and stenosis of the CFA can be dealt with CFA cutdown by vascular surgery. The cutdown procedure, despite increasing the success rate of EVAR, carries a low degree of complications such as seroma or lymphocele, hematoma, bleeding, blood transfusion, vessel dissection, femoral nerve injury, infection, delay in wound healing, and scar tissue.⁸⁵ The diameter of the EIA plays an important role in device insertion and removal. A rupture of EIA can result in a catastrophic event requiring covered stent placement, transfusion, emergency vessel repair, or death. EIA rupture is associated with a higher mortality rate and length of stay.⁸⁶

One of the limitations for EVAR can be related to access caused by small-caliber arteries, calcification, and stenosis. These limitations can cause significant complications such as vessel dissection, perforation, rupture, and sudden occlusion. Emergent management of these complications in an urgent setting of EVAR can result in significant mortality and morbidity. CIA conduit can be a creative and very useful access modality for large-bore sheath management during EVAR.⁸⁷ However, a CIA conduit needs retroperitoneal incision, blood transfusion, GA, and prolonged stay in the hospital. A CIA conduit can be placed using a 8- to 10-mm Dacron patch sutured to the CFA (Figure 23.10).

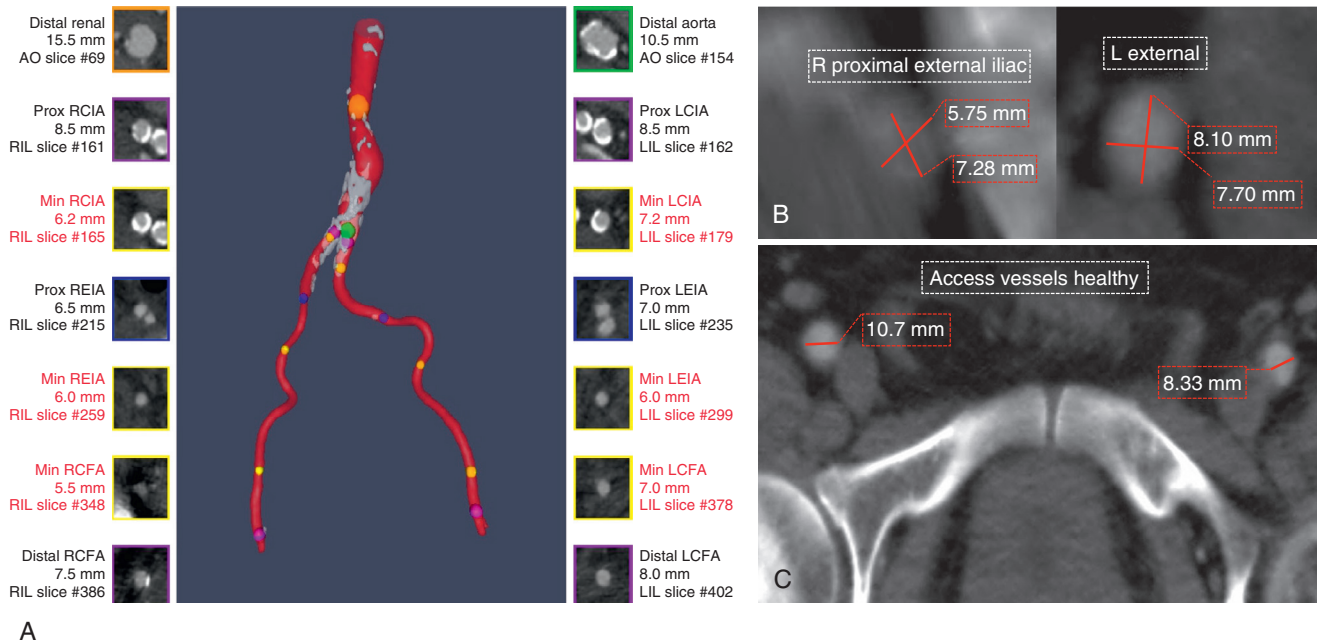


FIGURE 23.9 Computed tomography angiography measurements of the access vessels. **A**, Measurements using M2S software. **B**, Individual external iliac artery measurements. **C**, Common femoral artery measurements. AO, aorta; RCIA, right common iliac artery; RIL, right internal iliac artery; REIA, right external iliac artery; RCFA, right common femoral artery; LCIA, left common iliac artery; LIL, left internal iliac artery; LEIA, left external iliac artery; LCFA, left common femoral artery

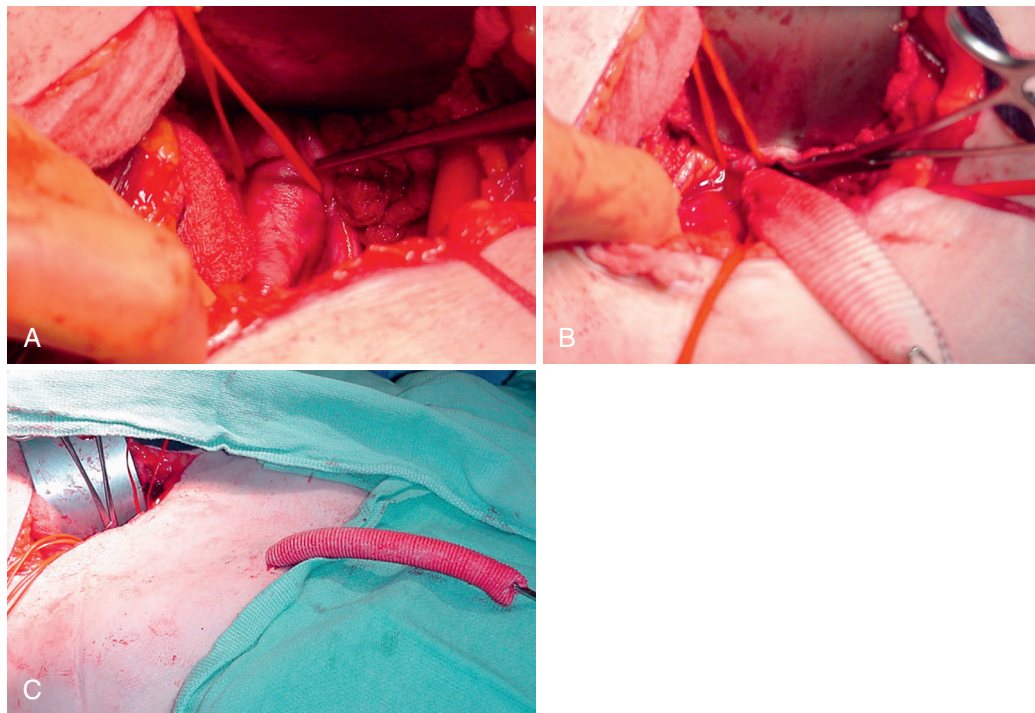


FIGURE 23.10 Access management for endovascular aneurysm repair with an iliac artery conduit. **A**, Retroperitoneal incision to demonstrate the common iliac artery exposure. **B**, Dacron graft sutured to the common iliac artery. **C**, Dacron graft tunneled to the skin surface for access.

Percutaneous Endovascular Aneurysm Repair

The advent of arterial access closure devices has enabled percutaneous endovascular aneurysm repair (PEVAR). PEVAR has demonstrated the low incidence of early and late access site complications.^{88,89,90} The “preclose” technique for percutaneous access and closure uses Perclose ProGlide Suture Mediated Closure System (ProGlide SMC,

Abbott Vascular) and is as follows (Figure 23.11). MANTA is a percutaneous large-bore vascular closure device that uses a collagen plug-based approach to provide hemostasis. The SAFE MANTA study evaluated the safety and effectiveness in a prospective, single-arm, multicenter trial in patients undergoing endovascular interventions for TVAR, EVAR, and thoracic endovascular aortic repair

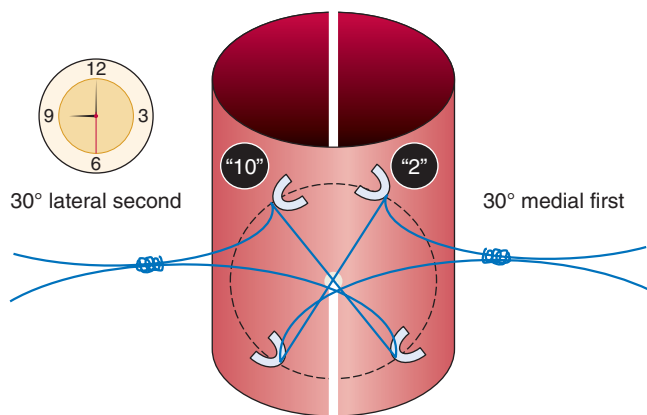


FIGURE 23.11 Schematic cartoon concept of “preclose” using a ProGlide SMC for percutaneous access and closure. The two Preclose ProGlide sutures are deployed 30 degrees medial first and 30 degrees lateral second. (Courtesy of Dr. Z. Kracjer, Texas Heart Institute.)

(TEVAR). A total of 263 patients enrolled underwent EVAR ($n = 51$) and TEVAR ($n = 2$), and this subgroup was analyzed. The technical success rate was 98% of EVAR or TEVAR cases, 1 (1.9%) access site stenosis was noted, and 14 (5.3%) in the remainder of the Transcatheter Aortic Valve Replacement (TAVR) group. One pseudoaneurysm was noted at discharge, 1 at 30 days follow-up, and 1 at 60 days.⁹¹

The step-by-step approach to the “preclose” technique for PEVAR (Video 23.1) is as follows:

1. Select the CFA that is free of calcium, plaque, and stenosis based on CT scan imaging in cross-sectional and sagittal views.
2. Use a micropuncture needle for access and obtain a sheath angiogram to ensure mid-CFA access at the start of the case.
3. Advance the first ProGlide over a 0.035-inch guidewire until bleeding is noted from the side port; then remove the guidewire.
4. Rotate the closure device to 30 degrees medially and deploy the suture. Carefully retrieve the monofilament sutures and secure them with a rubber hemostasis.
5. Replace the guidewire into the ProGlide device via the wire port and remove the device, maintaining the wire access.
6. Deploy a second ProGlide rotating the device 30 degrees laterally over the same guidewire.
7. Insert an 8- to 10-Fr sheath for hemostasis and secure.
9. If large-bore access is needed on the contralateral side, the same steps are repeated to secure the Preclose ProGlide sutures.
10. At the end of the EVAR procedure, carefully guide the knot pusher over the top of the arterial puncture and tighten the knot and then lock the suture.
11. If a suture breaks, maintain wire access and deploy a second device.
12. Remove the guidewires when reasonable hemostasis is achieved and cut the sutures followed by manual pressure for 5 minutes if needed.

Anterior wall calcification of the access artery and severe fibrosis have been shown to be predictors of vessel failure, but the sheath size and obesity have not.⁹² Mousa

et al. have shown that operator learning curve for the preclose technique, vessel calcification, age, and female gender are predictors of failure of PEVAR and the need for open conversion.⁹³ The PEVAR trial was a multicenter, randomized prospective trial that compared the percutaneous “preclose” technique with surgical femoral cutdown for EVAR (SEVAR).⁹⁰ A total of 192 patients were enrolled, including 41 in the roll-in phase, and 151 patients were randomized to PEVAR or SEVAR. The 30-day ipsilateral access site vascular complication rate was 6% in the PEVAR group compared with 10% in the SEVAR group ($P = .0048$). The total procedure time and time to hemostasis was shorter in the PEVAR group compared with the SEVAR group.

Renal Artery Anomalies

Horseshoe kidney, accessory renal arteries, and ectopic origin of renal artery can affect EVAR. If the aortic neck length distal to the lowest accessory or renal artery meets the criteria for the device IFU, EVAR can still be pursued. Occasionally, a small accessory renal artery (diameter <2.5 mm) may be covered during EVAR if it supplies a small amount of renal parenchyma. The largest series of outcomes of accessory renal artery coverage during EVAR was studied by Greenberg et al.⁹⁴ A total 426 patients who underwent EVAR were identified; accessory renal artery was noted in 69 patients. A total of 35 patients had accessory renal artery covered versus 29 patients with accessory renal preservation. Renal infarction occurred in 84% of kidneys that had accessory renal artery covered. It is important to note that there was no significant decline in renal function between the two groups and no difference in need for antihypertensive drugs, secondary interventions, and rate of endoleak. Patients with a horseshoe kidney can undergo successful EVAR with careful preoperative CT planning despite the anatomic challenges^{95,96} (Figure 23.12).

Food and Drug Administration-Approved Devices for Endovascular Aneurysm Repair (Figure 23.13)

1. Ancure device (Guidant): withdrawn from US market in 2003
2. Medtronic Endurant, Endurant II Aorta-Uni-Iliac (AUI) stent graft system, Talent, and AneuRx (Medtronic)
3. Gore Excluder, Gore C3 delivery system for Excluder iliac branch endoprosthesis and Conformable AAA endoprosthesis (W.L. Gore and Associates)
4. Zenith Flex AAA endograft and Zenith Fenestrated AAA endovascular graft (with adjunctive Zenith Alignment stent) (Cook Medical)
5. Endologix
 - a. Powerlink System, AFX, and AFX DuraPly (Endologix): Class I recall by the FDA because of increased risk for type 3 endoleaks
 - b. AFX 2 is available with a caution letter from the FDA (“Implanting physician should justify device use and explain to the patient the device preference suitability”)
 - c. OVATION iX (abdominal stent graft system, Endologix): withdrawn from market in 2020
 - d. Alto abdominal stent graft system (Endologix)



FIGURE 23.12 **A** and **B**, Accessory renal artery covered during endovascular aneurysm repair. **C**, Low origin of right renal artery in a patient with abdominal aortic aneurysm.

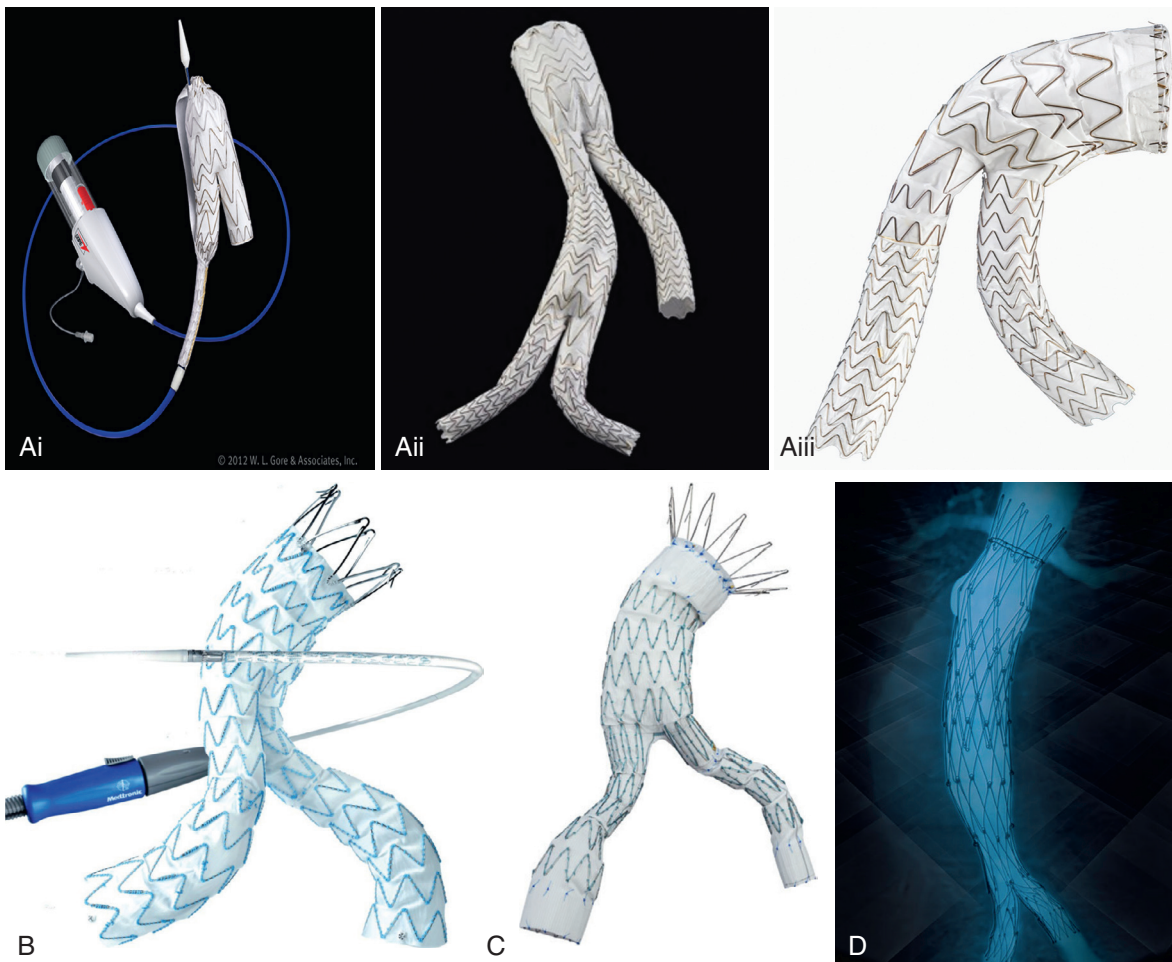


FIGURE 23.13 Endovascular aneurysm repair (EVAR) devices approved by the Food and Drug Administration. **Ai**, Gore Excluder. Confirmable (**Aii**) and bifurcated (**Aiii**) iliac limb system (W.L. Gore and Associates). **B**, Medtronic Endurant II (Medtronic). **C**, Zenith Flex AAA endograft (Cook Medical). **D**, Endologix AFX and VELA System (Endologix).

Continued

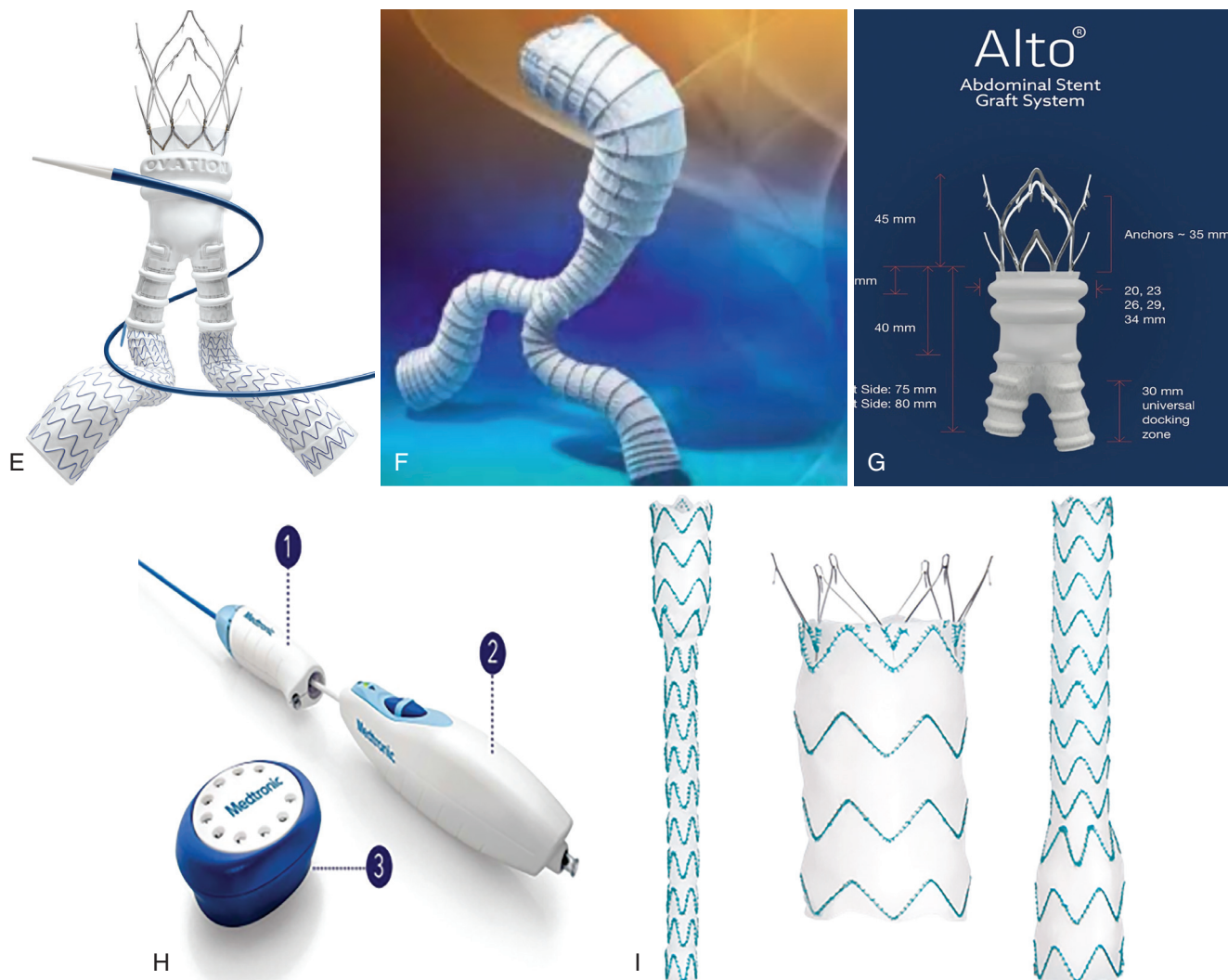


FIGURE 23.13, cont'd **E**, OVATION abdominal stent graft system (Trivascular). **F**, Aorfix Flexible AAA Stent Graft System (Lombard Medical). **G**, Alto, (Endologix LLC), **H**, EndoAnchors (Medtronic), **I**, Terumo Aortic (Bolton Medical).

6. Aorfix flexible stent graft system (Lombard Medical): US operations closed in 2016. Europe has availability of fenestrated EVAR grafts.

7. Terumo Aortic Company (Bolton Medical): TREO abdominal stent graft system

The Cordis (Incraft) AAA stent graft system is premarket approval (PMA) approved but not yet marketed in the United States.

Most of the EVAR devices are modular two- or three-piece systems, except for the Endologix Powerlink System, which is a unibody bifurcated device. The basic EVAR stent graft has four components:

- Delivery system
- Main body of the graft or aortic unibody
- Graft limbs and iliac extensions
- Aortic cuffs and extensions

The majority of the grafts rely on distal fixation at iliac artery and proximal fixation at the infrarenal or suprarenal aorta. The Endologix device relies on anatomic fixation at distal aortic bifurcation and active seal with the graft material. The ALTO device provides a seal by hollow rings in the fabric that are expanded by polymer injection after

deployment (Table 23.3). The Gore conformable delivery system helps to deploy infrarenal AAA Gore endoprosthesis in an angulated neck (<60 degrees).

- Branched iliac device: The Gore branched iliac device, in selected cases, can treat patients with internal iliac artery aneurysms in conjunction with treating AAA. The iliac branched device preserves flow into the internal iliac artery by placing a minor bifurcated limb inside the joint iliac artery limb of the AAA graft.
- EndoAnchors (Medtronic) can be adjuvant to complex AAA such as the reverse tapered neck, juxtarenal aneurysm, borderline neck diameter, and persistent type Ia endoleak. The EndoAnchors contain helical screws that can be loaded into a flexible catheter. The catheter tip can be rotated or flexed and extended to oppose the inner fabric of the AAA abdominal graft system below the renal arteries. The helical screws are then mechanically deployed to anchor the graft to the aortic wall without causing a perforation. EndoAnchors can secure the graft and prevent type Ia leak, aneurysmal sac expansion, and graft migration.

TABLE 23.3 Food and Drug Administration-Approved Available Endovascular Aneurysm Repair Devices with Graft Material, Stent Support, and Individual Characteristics

EVAR DEVICE	GRAFT MATERIAL	STENT SUPPORT	INFRARENAL OR SUPRARENAL	ANCHOR HOOKS
Medtronic Endurant II, Talent, AneuRx	Polyester weave	Nitinol stents outside	Suprarenal and infrarenal	Yes
Gore Excluder, confirmable and Iliac branched device	ePTFE	Nitinol stents	Infrarenal	No
COOK Zenith	Polyester weave	Stainless steel stents outside	Suprarenal	Yes
Endologix AFX 2	DuraPly	Cobalt chromium endoskeleton	Suprarenal and infrarenal	No
ALTO	PTFE	Nitinol	Suprarenal	Yes
Aorfix	Woven polyester	Nitinol wire	Infrarenal	Yes
Terumo Aortic	PTFE	Nitinol wire	Infrarenal	yes

ePTFE, Expanded polytetrafluoroethylene; EVAR, endovascular aneurysm repair; PTFE, polytetrafluoroethylene.

Fenestrated Stent Grafts and Physician-Modified Grafts for Complex Aneurysms

The evolution of EVAR to manage complex aneurysms involving the visceral arteries led to the development of fenestrated endovascular stent grafts (f-EVAR). The lack of adequate proximal neck diameters, length, angulations, taper, reverse taper, or visceral artery involvement can limit the use of traditional EVAR in up to 40% of patients.⁹⁷ Greenberg et al. reported the use of branched endograft for thoracoabdominal aneurysms.⁹⁸ In this prospective study involving 406 patients with thoracoabdominal aneurysms, 227 patients with juxtarenal aneurysms were noted. The patients who underwent endovascular approach were matched against those undergoing open surgical repair. The short-term mortality rate and paraplegic rate were similar at 30 days. In the endovascular group, late ruptures were noted to be in 0.8% of patients at 18 months. Four patients died because of device component separation, aneurysm rupture proximal to endovascular repair, and failed surgical polyester graft distal to the repair. The fenestrated branch patency rate for patients who received reinforcement using a balloon-expandable covered stent was 97.8% at 15 months. The study demonstrated technical feasibility of the procedure and low mortality and morbidity.

Greenberg et al.⁹⁹ evaluated the results of the Zenith endovascular fenestrated stent graft for 30 patients with short necks and mean aneurysm diameter of 61 mm. The study was conducted at five centers over a period of 1 year. The implant was successful in all patients; there were no aneurysm-related deaths and no rupture. A total of six renal-related events, including stenoses, occlusions, and infarcts, were seen, and one patient had device migration. Figure 23.14 shows a case of fenestrated graft used in an AAA with short neck using the VENTANA system (Endologix). The VENTANA system was taken off the market.

Physician-Modified Grafts for Complex Aneurysms

In cases of complex aneurysms such as a short neck, reverse taper, or large diameter of the neck (>32 mm), physicians may opt to modify the graft to perform EVAR. Such modifications may involve on table fenestration of the graft using a cautery based on preplanning CT scan imaging (Figure 23.15).

Chimney and snorkel techniques are used in short neck or juxtarenal aneurysms at high risk for open repair. Bilateral simultaneous renal covered stents with AAA stent grafts can be beneficial. Gutter leaks and continued growth of aneurysms are common. The long-term results of such snorkel and chimney grafts have yet to be discovered. Some thoracic and abdominal aneurysms can be treated with a snorkel by placing covered stents in the celiac and superior mesenteric arteries.

Step-by-Step Deployments of Endovascular Aneurysm Repair Stent Graft (Video 23.2)

Thoracoabdominal Aneurysm Treated with Snorkel Technique

An 84-year-old patient with a history of chronic tobacco use for 50 years, one pack per day, presents with incidental finding of large abdominal aneurysm of 7.0 cm noted at an ultrasound screening program. The age, comorbidities, and patient preference were considered, and EVAR was planned. A Gore C3 delivery system for Excluder (W.L. Gore and Associates) was chosen based on iliac dimensions and the low profile of the device (Figure 23.16).

The step-by-step deployment of EVAR stent graft is:

1. Under MAC, the patient was given conscious sedation.
2. Bilateral CFA access was obtained with an ultrasound guidance and micropuncture needle (described previously).
3. Bilateral preclose technique was used with the ProGlide closure device (described previously).
4. An 18-Fr sheath was placed via the right CFA under fluoroscopy, and heparin was given to keep the activated clotting time (ACT) above 250 seconds.
5. A pigtail catheter was placed via the contralateral CFA, and bilateral renal arteries were marked on the screen.
6. The main body of the device chosen was placed via the 18-Fr sheaths below the left renal artery, and the device was deployed.
7. The contralateral limb was cannulated with a wire and catheter.
8. The contralateral limb length was measured from the gate of the limb to the hypogastric artery using a marker pigtail catheter.

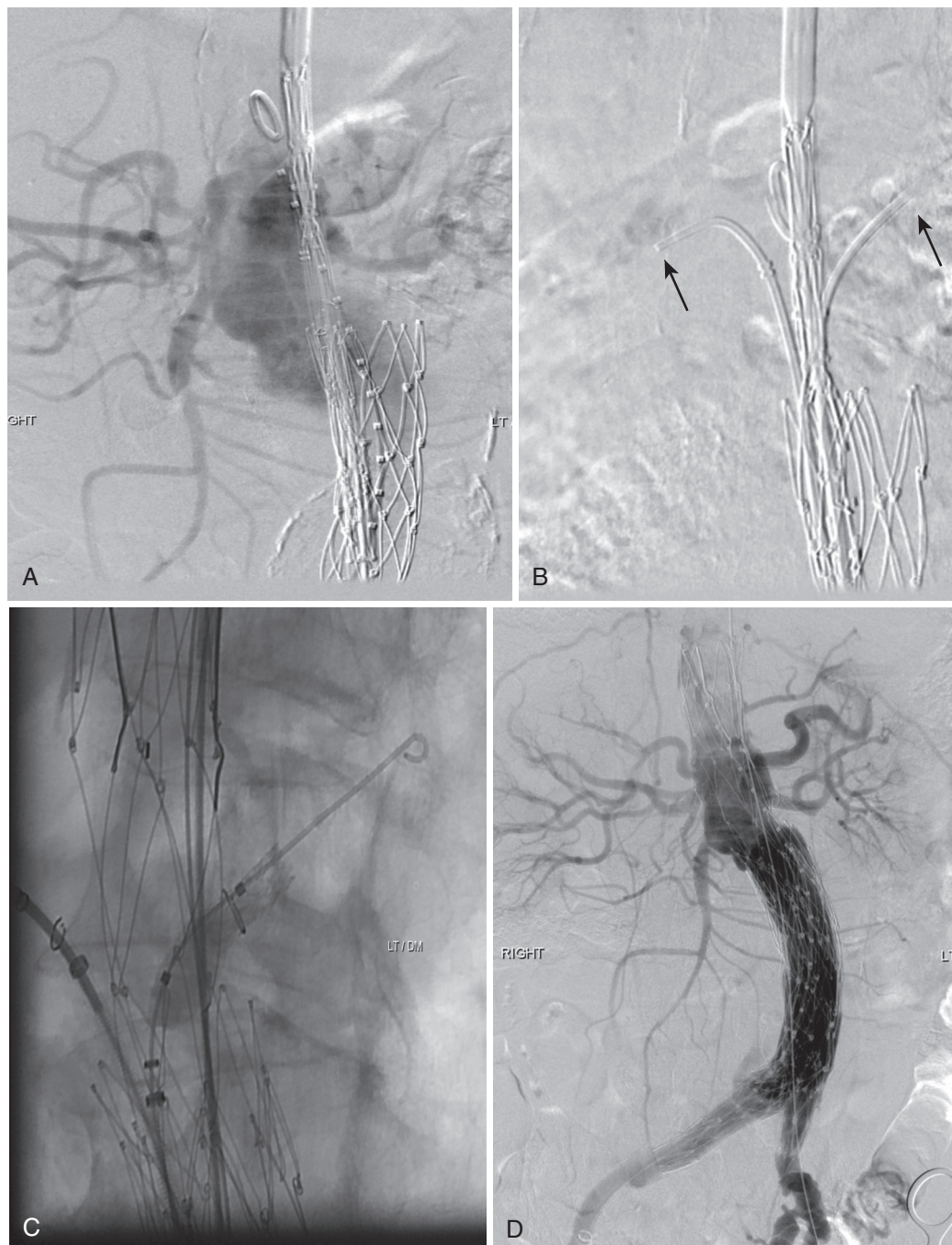


FIGURE 23.14 A case of fenestrated graft used in an abdominal aortic aneurysm with a short neck using the VENTANA system (Endologix). **A**, Angiogram shows a short neck. **B**, Cannulation of bilateral renal artery. **C**, Deployment of suprarenal portion of the graft. **D**, Final angiogram to show patency of the renal artery.

9. The contralateral limb was deployed using a 12-Fr sheath.
10. The graft overlap and proximal and distal ends were dilated with a molding aortic balloon.
11. Final angiogram showed successful exclusion of the aneurysm with no endoleak.
12. The bilateral CFA preclose sutures were approximated to obtain hemostasis.

The patient was ambulated at 6 hours postprocedure and monitored overnight before discharge at 24 hours. The patient will be followed in the vascular clinic at 30 days, 6 months, and 1 year with CT.

Surveillance and Complications

Surveillance for aortic neck dilation, device migration, graft occlusion, and material breakage such as stent fracture is essential after EVAR and is performed at 1 month, 6 months, and then annually.

Intraoperative Complications

Most common intraoperative complications are related to vascular access such as iliac rupture, vessel dissections, occlusions, and embolization. Iliac artery rupture can be lethal to the patient if not immediately recognized and treated. Iliac artery rupture can be managed with an endovascular

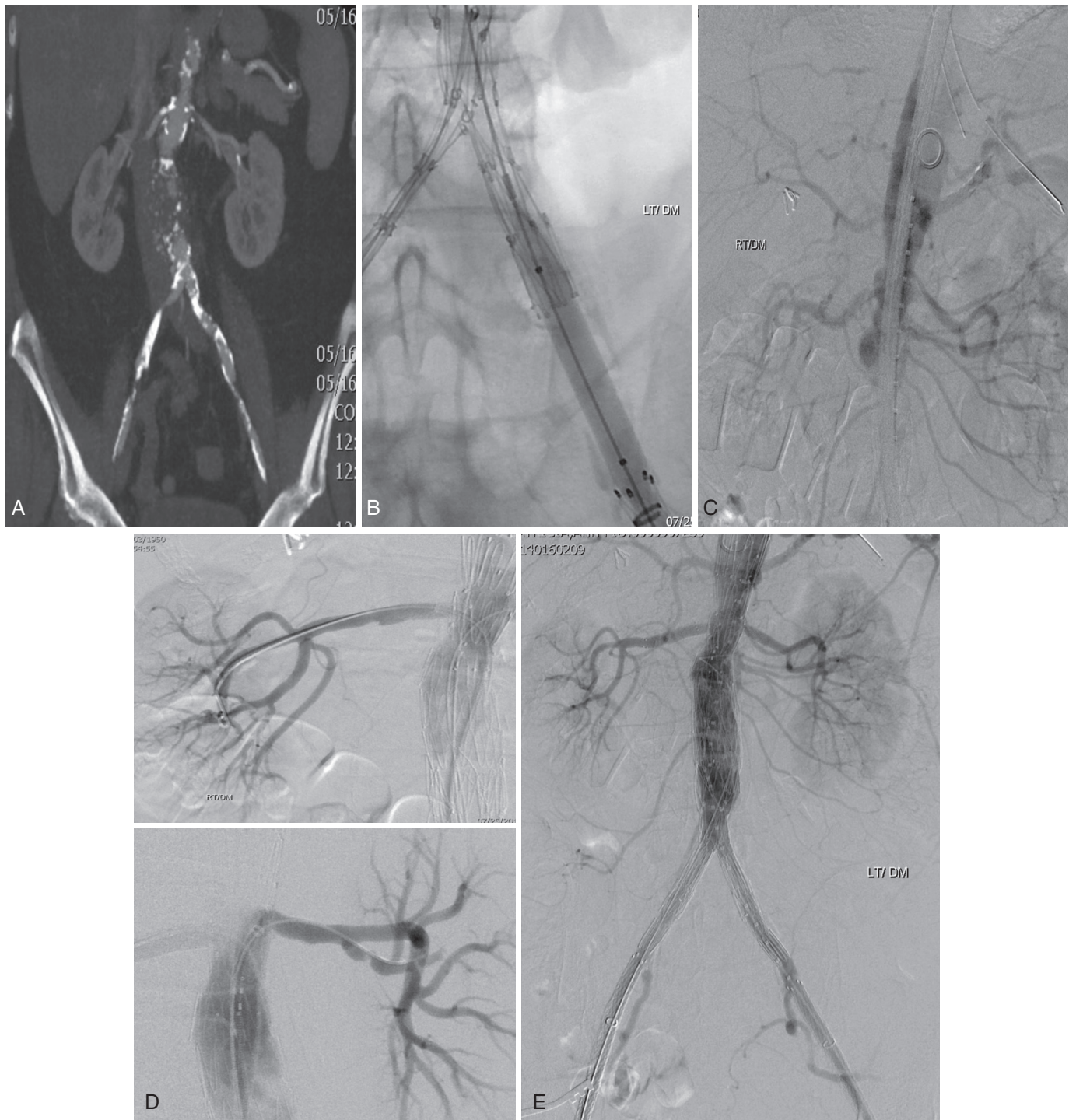


FIGURE 23.15 A case example of bilateral renal artery on table fenestration. **A**, Abdominal aortic aneurysm with a short neck (<5 mm) and reverse taper. **B**, Placement of the Endologix main body. **C**, A thoracic Cook TX 2 piece is used for fenestration. **D**, Left and right renal artery fenestration. **E**, Final angiogram. *PSA*, Pseudoaneurysm; *SMA*, superior mesenteric artery; *TEVAR*, thoracic endovascular aortic repair.

approach. A contralateral aortic balloon tamponade and immediate placement of covered stent or graft to seal the perforation can be lifesaving. If the rupture cannot be contained or controlled, emergency surgical repair may be needed (Figure 23.17). Arterial occlusion, stenosis, and dissection are usually treated with endovascular balloon dilation or stent placement. Rarely, an iliac vessel occlusion or flow-limiting dissection may require bifurcated EVAR limb conversion to an aorta unilimb stent graft and a femoral-femoral bypass.

Significant atheroembolism requires embolectomy with adjunct stenting and rarely, femoral-distal arterial bypass. The other early complications are intraoperative myocardial infarction, arrhythmias, renal artery embolization, and inadvertent partial or full coverage of renal artery.

Endoleak

Endoleak can occur immediately (types Ia/Ib and III) after procedure or develop in a few months to a few years

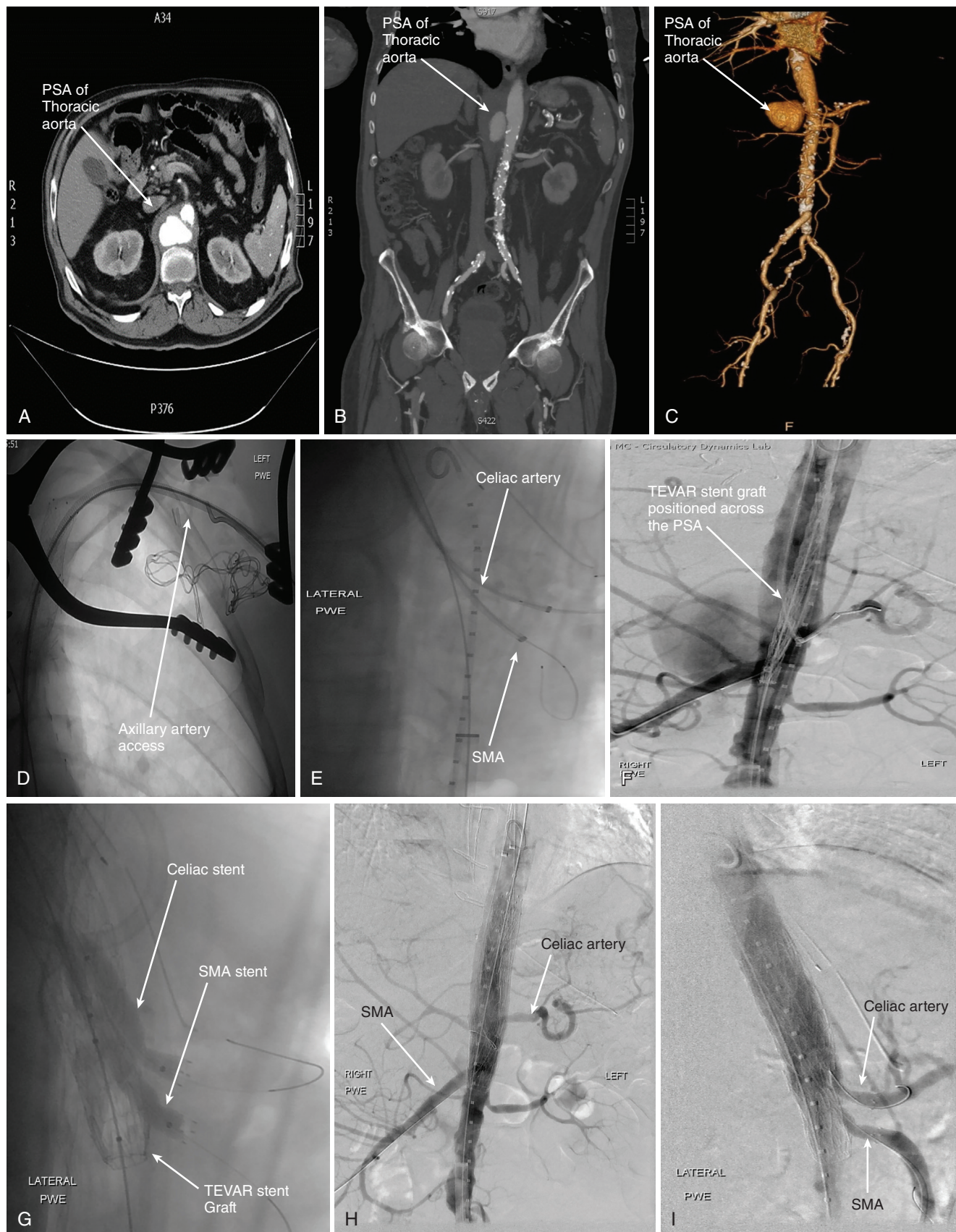


FIGURE 23.16 A–C, A 75-year-old man with a past medical history of dementia, coronary artery disease, stroke, hypertension, and chronic obstructive pulmonary disease presented with abdominal pain. Computed tomography angiography of the abdomen revealed a 7.2-cm pseudoaneurysm (PSA) in the descending thoracic aorta just below the celiac and the superior mesenteric artery (SMA). Thoracic endovascular aortic repair (TEVAR) stent graft covers the PSA, and a snorkel procedure was performed for the celiac artery and SMA. D, Left axillary cutdown for access. E, Selective wiring of the celiac artery and SMA. F, TEVAR stent graft positioned across the PSA. G, Simultaneous balloon dilation of the TEVAR stent graft, covered stent in SMA and celiac artery. H, Final thoracic aorta angiogram anteroposterior view. I, Lateral view angiogram showing exclusion of thoracic PSA and patent celiac and SMA stents.

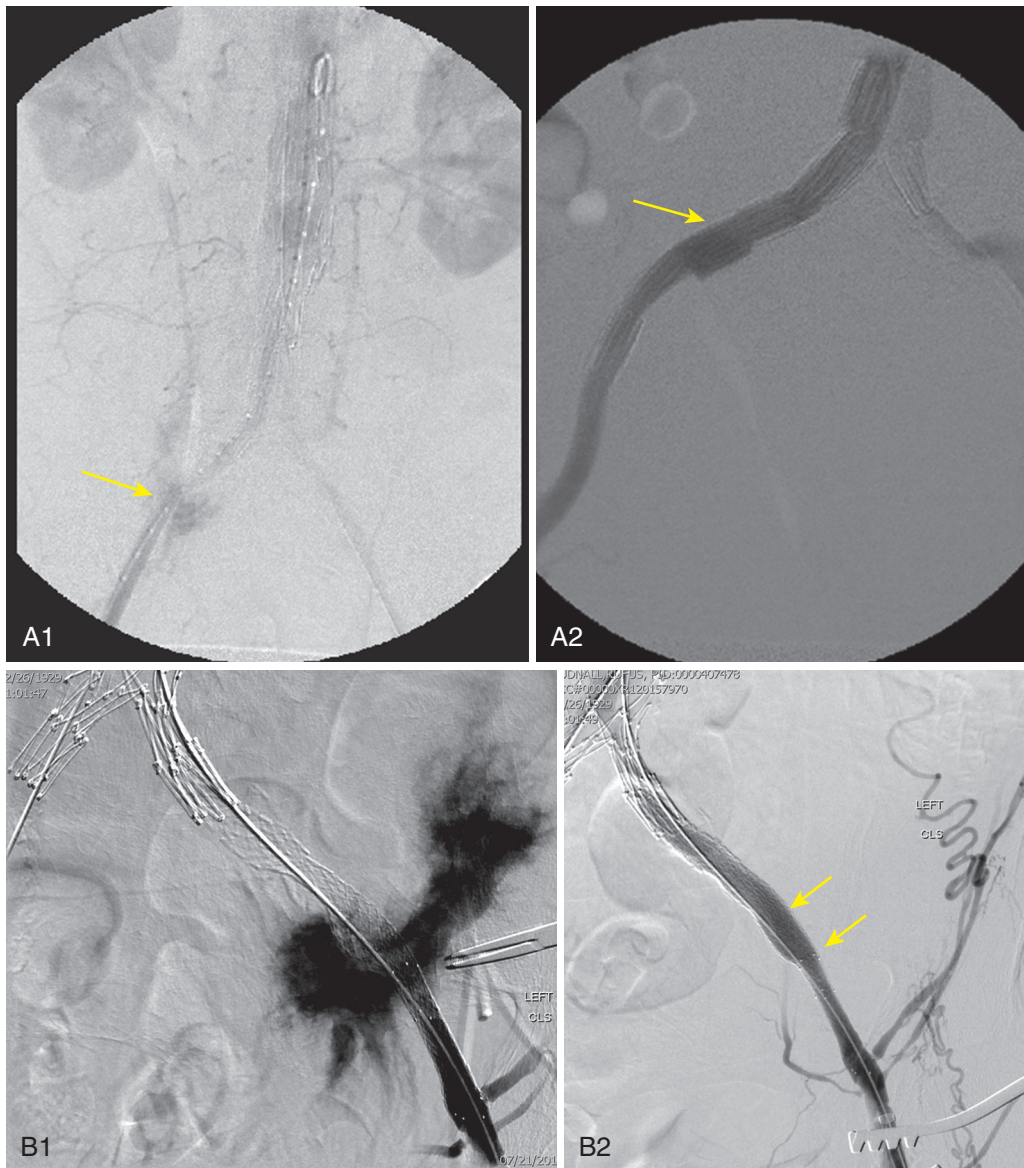


FIGURE 23.17 Complication: the external iliac rupture during endovascular aneurysm repair treated with a stent graft limb (**A1** and **A2**) and a covered stent (**B1** and **B2**) at follow-up.

(types II and IV) after an EVAR. An endoleak permits flow from native aorta into the aneurysmal sac and poses a threat for continued AAA enlargement and future rupture. Type I and III leaks should be immediately addressed before the patient leaves the endovascular or operating room. Type II and IV endoleak are usually detected during CT scan follow-up and can be treated electively. Late endoleak threatens the durability of EVAR because of persistent blood flow and resultant pressure in the aneurysm sac. CT is considered the gold standard for detecting and categorization of endoleak, although ultrasound and MRA are being studied as well.¹⁰⁰ The various types of endoleak according to the site and origin of blood flow are described in the management and follow-up of EVAR¹⁰¹ (Table 23.4).

TYPE I ENDOLEAK. Type I endoleak occurs because of inadequate or poor sealing of the endograft at the proximal or distal attachment sites. The antegrade blood flow from

systemic pressure results in continued sac enlargement and increases the risk of rupture. Hence, conservative management has no role for type I endoleak; most of these should be identified and treated at the time of EVAR implantation. The proximal endoleak often occurs because of hostile neck anatomy, less than ideal dimensions, and poor patient selection.¹⁰² A molding balloon inflation at the proximal attachment site can help in sealing the type I endoleak, and if this maneuver fails, careful evaluation of the infrarenal neck portion may reveal room for additional aortic cuff placement. EndoAnchors are helical stainless steel screws deployed via endovascular approaches to tack the proximal edge of the graft below the renal arteries. The helical screws penetrate the graft and stay embedded into the aortic tissue wall without causing a perforation. Persistent type I endoleak caused by the graft not well opposed at the neck can be treated with a Palmaz stent (Cordis)

TABLE 23.4 Endoleak Classification, Features, and Treatment Options

CLASSIFICATION	FEATURES	TREATMENT
Type I	Proximal or distal graft attachment zone	Balloon dilation, extension, or cuff Embolization in case of patent hypogastric artery EndoAnchors may help type Ia leak
Type II	The aneurysm sac fills by retrograde flow from filling of the aneurysm sac by retrograde flow from patent lumbar vessels, intercostals, or the IMA	Conservative Coil embolization of the lumbar and IMA in case of sac expansion, transcaval embolization of the AAA sac
Type III	The inadequate seal between modular graft components leads to leak If modular graft components, type IIIa, and if graft component is defective, separation or erosion For type IIIb, graft component separation or graft erosion	Secondary endograft placement to seal the defective or separated graft
Type IV	Leak through the stent graft caused by graft porosity	Conservative rare in the present graft era
Type V	Sac enlargement without a defined source, also known as endotension	If post-EVAR sac measures >1.0 from baseline before EVAR, then realignment of the graft

AAA, Abdominal aortic aneurysm; EVAR, endovascular aneurysm repair; IMA, inferior mesenteric artery.

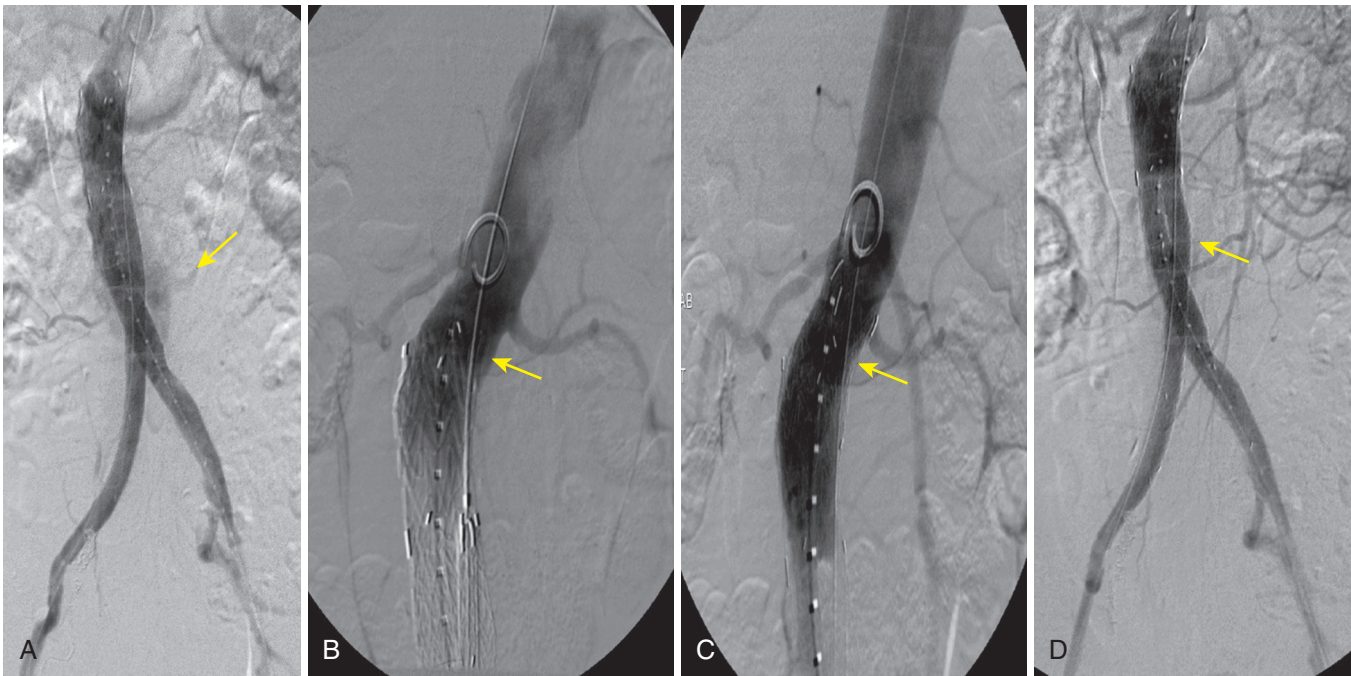


FIGURE 23.18 Type I endoleak and endovascular management. **A**, Type 1 endoleak. **B**, The infrarenal neck shows graft migration. **C**, Additional aortic cuff placed in the infrarenal portion. **D**, Final angiogram showing no further endoleak.

placed at the renal artery level extending to the infrarenal neck.¹⁰³ Failure of endovascular techniques to correct the endoleak requires open repair¹⁰⁴ (Figure 23.18).

TYPE II ENDOLEAK. Type II endoleak can occur because of retrograde perfusion of the aneurysm. The retrograde flow is usually from patent lumbar arteries, iliac-lumbar collaterals, or patent IMA via marginal artery of Drummond. Type II leaks are commonly noted in early postoperative CT imaging in up to 10% to 20% of cases. The majority ($\leq 80\%$) of these type II leaks have shown to spontaneously resolve within 6 months of the graft implant.^{98,99} Type II endoleaks are low pressure and slowly enlarge the aneurysmal sac over several years and hence have a low likelihood of rupture. The indications for intervention of type II endoleak

are aneurysmal sac expansion and persistent endoleak (Figure 23.19). Various techniques and treatment options for type II endoleak management are described in the literature¹⁰⁵ as follows:

- Coil embolization of the inflow and outflow source of iliac-lumbar collaterals pathway and the origin of IMA via the marginal artery of Drummond
- CT- or fluoroscopy-guided direct aneurysmal sac puncture and placement of polymer material in the sac
- Transgraft puncture using laser and placement of glue or polymer material into the aneurysmal sac
- Laparoscopic ligation of lumbar branches

A novel option to treat persistent type 2 endoleak from the lumbar is transcaval embolization. The procedure

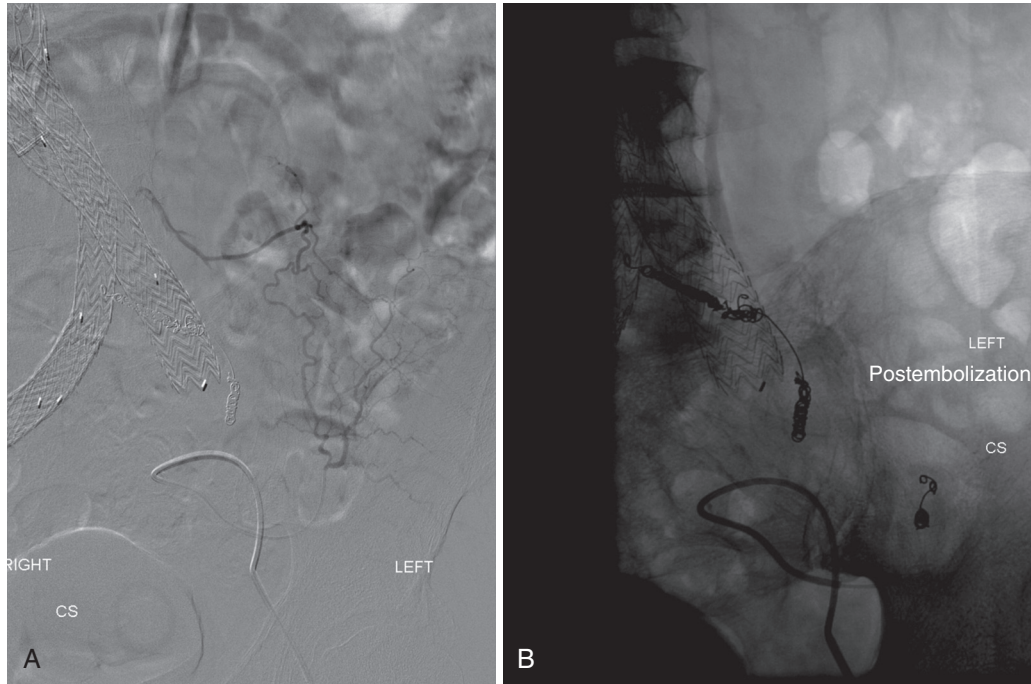


FIGURE 23.19 A and B, Type II endoleak treated with coil embolization of lumbar collaterals. CS, compressed sensing.

involves transcaval access of the aneurysmal sac and embolization of lumbar arteries with coil or Onyx (ethylene vinyl alcohol copolymer; ev3, Covidien). A retrospective review of patients who underwent transcaval embolization of type 2 leaks from lumbar arteries after EVAR in 2017 found that the average age of the patient was 82 years, 80% were male patients, the mean follow-up period from previous intervention was 5.5 years, and the average size increase from baseline was 1.2 cm. At 6 months, 90% of the patients showed a reduction in sac size. There were no complications of retroperitoneal bleeding, bleeding requiring transfusion, bowel injury, access site venous thrombosis, or death.¹⁰⁶

Case 3 of transcaval embolization of an aneurysmal sac to treat persistent type 2 endoleak is shown.

TYPE III ENDOLEAK. Type III endoleaks are caused by endograft fabric tear or separation of the device components, leading to high-pressure leak and aneurysmal enlargement or rupture. Improper sizing of iliac limbs can lead to kink in the graft, and subsequent device separation can result in type III endoleak. Aggressive ballooning and instrumentation can lead to iatrogenic graft material tear and subsequent endoleak (Figure 23.20). If type III leaks are noted during the implant, they should be corrected with the use of additional limb or cuff immediately. Some type III endoleaks are seen during late (4–10 years) follow-up on CT scanning. Such late leaks are usually caused by progressive enlargement of the neck or the aneurysmal sac, resulting in migration of the limb and separation of the components.

TYPE IV ENDOLEAK. This occurs mainly from older graft material with porosity, allowing slow oozing of the blood into the aneurysm sac. The recent improvements in the graft material and design have largely eliminated such leaks. Type IV endoleak can be treated with realignment of

the graft with newer stent graft with fabric that does not allow porosity.

Endotension

Endotension is pressurization of the aneurysm sac in the absence of endoleak. The exact cause of endotension is unknown. The transmission of pressure from the aorta to the aneurysm sac via thrombus layered between the aortic wall and the stent graft is one of the mechanisms for endotension.¹⁰⁷ The sac pressure measurement can be performed by selective catheterization of superior mesenteric artery, IMA, or internal iliac artery to demonstrate endotension.¹⁰⁸ A specific concise radiofrequency sensor (EndoSensor, CardioMEMS) has been developed and used in the clinical setting. APEX, (Accute pressure measurement to Confirm Aneurysm Sac Exclusion) a multicenter clinical trial, demonstrated accurate measurement of the sac pressure in 93% of patients.¹⁰⁹

Endovascular Aneurysm Repair Limb Occlusion

Early models of endograft with unsupported limbs caused limb occlusion or stenosis in about 24% of implants. The risk factors that are identified to develop iliac limb occlusions after EVAR are unsupported endografts, small diameter of the iliac artery, preexisting iliac stenosis, and extension of the graft into EIA.¹¹⁰ The occluded limbs or stenosis can be treated with an endovascular approach such as stenting with self-expanding stents.¹¹¹ During EVAR implantation, if endograft limb stenosis or occlusion or kinking is noted, additional evaluation such as IVUS is helpful. Limb thrombosis occurs during the early period of postimplant follow-up (2 months) in the majority of patients.¹¹² The clinical presentation includes acute limb ischemia, new onset of limb or buttock claudication, and atypical leg pains. Thromboses of limbs can be managed

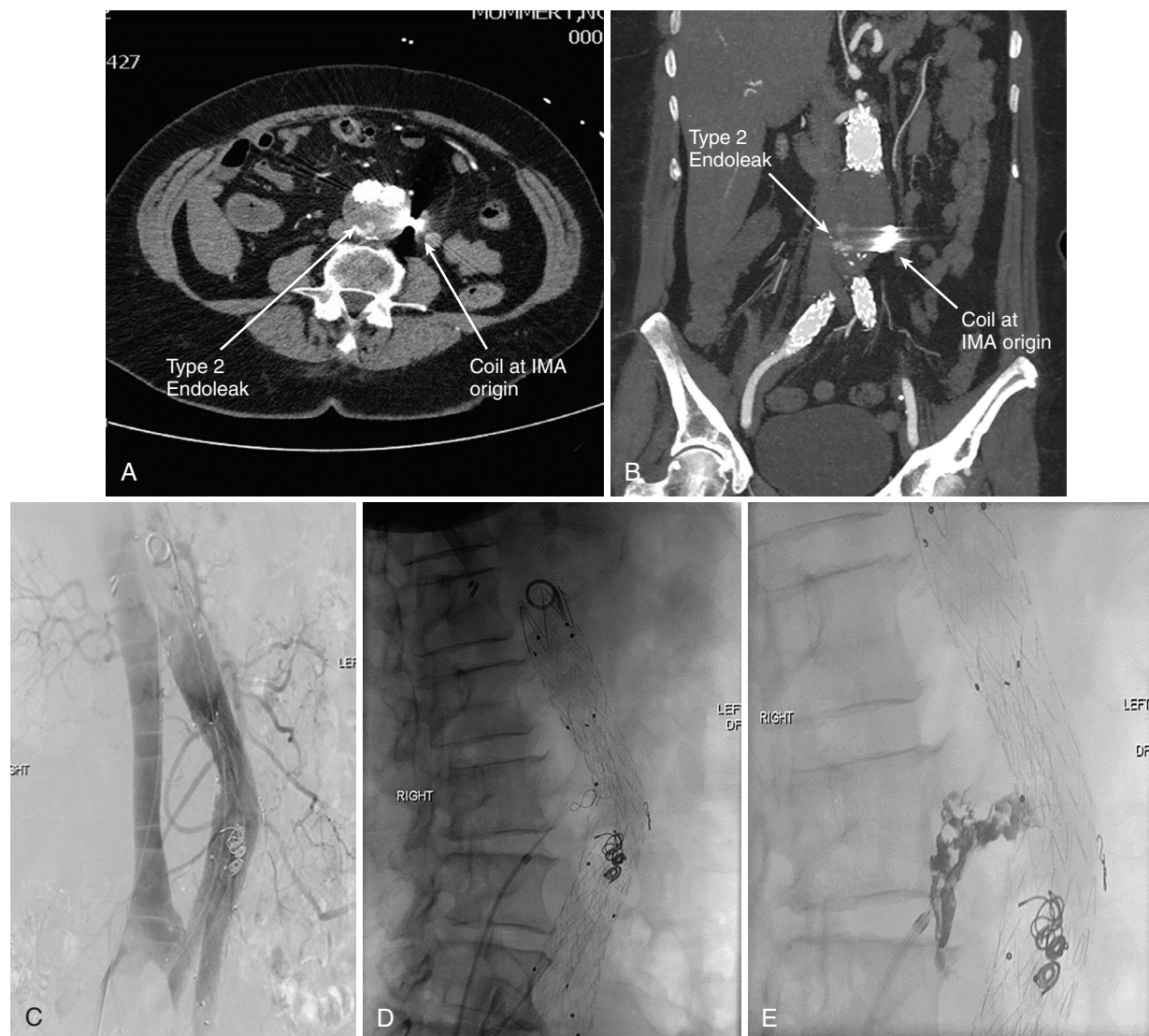


FIGURE 23.20 **A** and **B**, A 72-year-old patient had endovascular aneurysm repair (EVAR) for abdominal aortic aneurysm (AAA). At 5 years after EVAR, the AAA continued to grow. Delayed computed tomography images showed type II endoleak that persisted despite coil and Onyx embolization of the ostial inferior mesenteric artery (IMA) via the superior mesenteric artery. **C**, Baseline angiogram. **D**, Transcaval need puncture. **E**, Coil and Onyx embolization.

with endovascular techniques such as catheter-directed thrombolysis and adjunctive stenting. Surgical approach involves thrombectomy and, in some cases, femoral-femoral bypass (Figure 23.21).

Endovascular Stent Graft Migration

Device migration is defined by movement of the graft caudal or cranial more than 10 mm from the baseline after EVAR or at follow-up intervals. Device migration during the procedure is related to technique and anatomy. Such migration is corrected by additional cuff placement, EndoAnchors, or caudal mechanical traction of the graft when partially encroaching the renal arteries. Inadvertent coverage of renal or hypogastric arteries is treated with snorkel or fenestration or chimney stents. Acute device migration may cause catastrophic visceral occlusion and may need emergent aortorenal bypass.

The graft migration is usually noted during CT scan follow-up after EVAR. The graft can migrate cranially or

caudally based on involvement of the iliac limbs or aortic main body. The incidence of graft migration is 15% to 45% based on follow-up and definition of migration distance.¹¹³ Despite the use of endovascular stent graft, the proximal aorta and iliac artery distal to the graft dilates and facilitates graft migration. Some of the risk factors for endograft migration are baseline AAA dimension greater than 5.5 cm and aneurysmal neck dilation of greater than 10%.¹¹⁴ The mean age for graft migration is 1 year and 6 months, and half of these migrations need revascularization.¹¹⁴ Various techniques to treat graft migration are placement of aortic cuffs, limb extenders, and reinforcement with Palmaz stent. If the endovascular approach fails and the aneurysm continues to grow, an open surgical approach may be necessary. Various modifications to the endovascular grafts such as supra-renal stents, hooks, sealing rings, and distal aorta fixation devices have reduced the risk of graft migration (Figure 23.22).

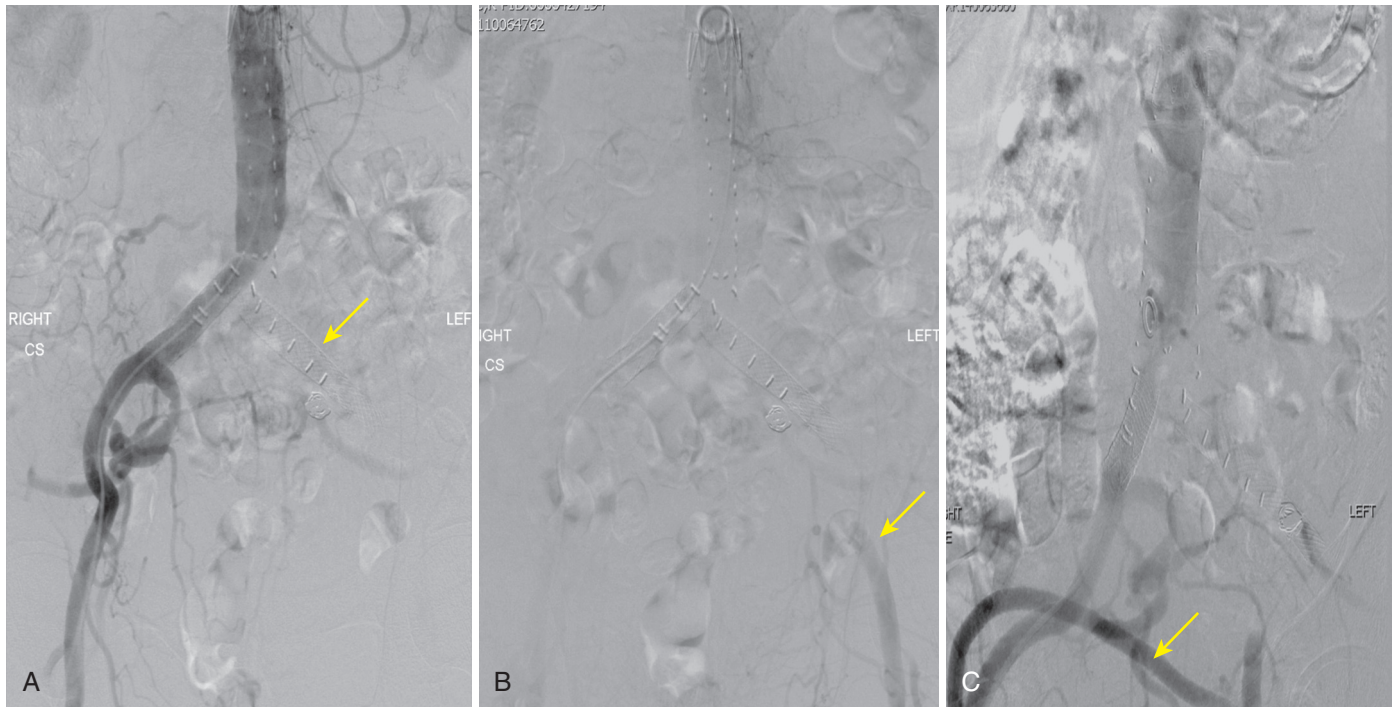


FIGURE 23.21 Endovascular aneurysm repair patient with limb occlusion caused by an unsupported left graft (A). Common femoral artery reconstitution (B) treated with femoral-femoral bypass (C). CS, compressed sensing.

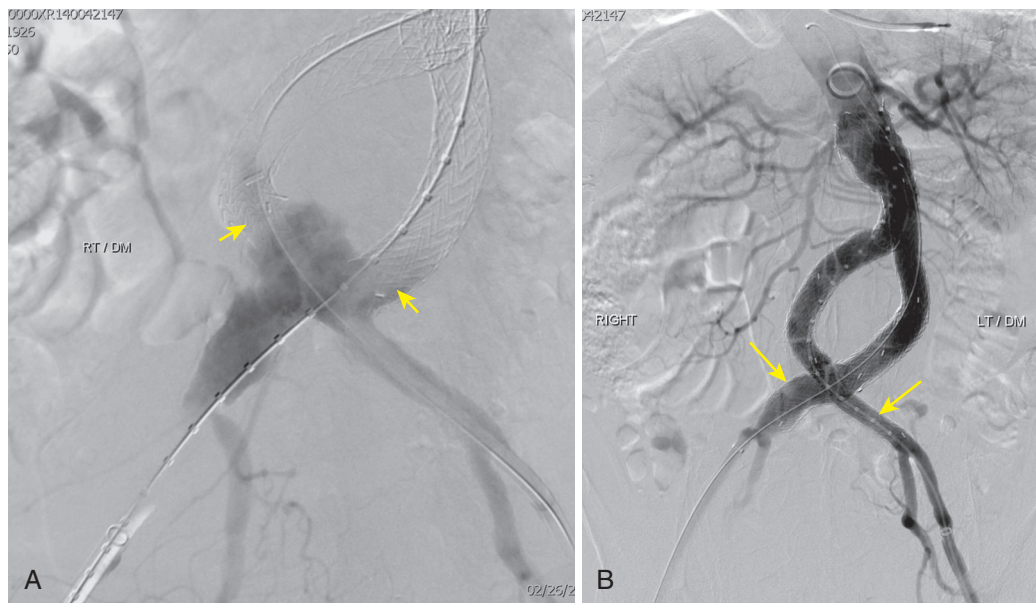


FIGURE 23.22 Migration of distal limbs cranial into the aneurysmal neck 6 years after implantation. A, The two iliac limbs are inside the aneurysmal sac. B, The two iliac limbs are extended into the common iliac artery.

Aneurysm enlargement is defined by an increase in aneurysm sac diameter greater than 5 mm at prespecified intervals, such as 6 months after EVAR. Continued enlargement is caused by endoleak or device migration and rarely from endotension. EVAR realignment is performed if symptomatic or the aneurysm sac is more than 10 mm from the baseline. Persistent and continued enlargement of the aneurysm sac mandates open repair to prevent rupture if feasible.

Postimplantation Syndrome

After the implantation of endovascular graft, a few patients develop an elevated white blood cell count and fever.¹¹⁵ A workup for an infectious cause in these patients is usually negative. Such patients may also have high C-reactive protein levels, but the clinical significance is unknown.¹¹⁶ Conservative management is sufficient in most cases of post-implantation syndrome. Persistent fevers, malaise, and positive cultures need aggressive workup and treatment.

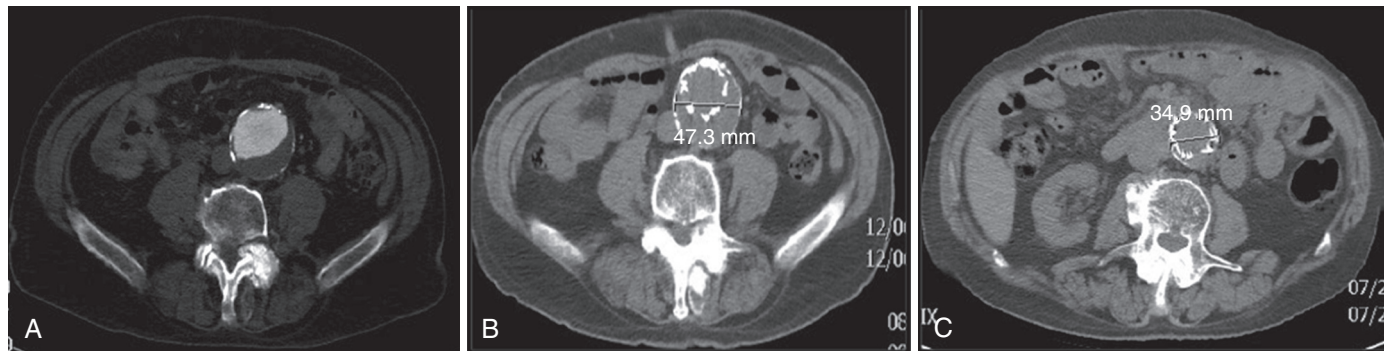


FIGURE 23.23 A, A 5.2-cm abdominal aortic aneurysm (AAA) at baseline. Endovascular aneurysm repair follow-up at 30 days (B) and at 6 months (C) showing shrinkage of size.

Contraindications to Endovascular Aneurysm Repair

Most contraindications are based on the suitability of AAA anatomy and EVAR device specifications. If the AAA anatomy in every aspect is outside the IFU for any of the device use, EVAR in these patients is contraindicated. EVAR in such patients increases the risk for complications and poor outcomes on follow-up such as endoleak, device migration, and increased secondary interventions. EVAR is performed to prevent rupture and prolong life; any condition that limits life expectancy to less than 6 months is a relative contraindication for elective EVAR. The implanting team of physicians should always be cognizant of the patient's cognitive function and quality of life, and these two factors should be considered before EVAR. In-depth unbiased discussion with the family and patient with a focus on the patient's best interest can be helpful in these situations. The presence of an active systemic infection is a high risk for seeding the endoprosthesis and thus may be considered a relative contraindication for EVAR. However, EVAR for a large symptomatic mycotic aneurysm in a patient with significant comorbidities may benefit in the short term. Patients with high-grade celiac and superior mesenteric stenosis are dependent on the IMA to provide perfusion to the large bowel. In these cases, EVAR and resultant coverage of the IMA may result in acute mesenteric ischemia or ischemic bowel and thus may be a relative contraindication for EVAR (see [Figure 23.16](#)).

Surveillance After Endovascular Aneurysm Repair

Surveillance and follow-up of patients with EVAR are very important because of late complications such as endoleak, graft migration, graft thrombosis, limb occlusion, distal embolization, limb ischemia, structural endograft failure, delayed aneurysm growth, and rupture. Patients with EVAR thus need lifelong surveillance to diagnose; identify impending graft failure; and if amenable, treat with an endovascular, or surgical, or hybrid approach ([Figure 23.23](#)).

The recommended standard of care EVAR surveillance includes serial contrast CT scans at 1, 6, and 12 months and yearly thereafter. These recommendations were based on the regimen in the clinical trials and approval process by regulatory agency such as FDA. Some of these surveillance regimens may be impractical and concerns are contrast-induced nephropathy, cumulative dangers of radiation exposure over a lifetime, and high costs.^{117,118}

Noll et al.¹¹⁹ in a long-term follow-up study of EVAR patients identified that surveillance regimens account for

30% to 35% of the total costs of EVAR. Sternbergh et al.¹¹⁰ in a 5-year follow-up of the US Zenith multicenter trial identified an improved long-term freedom from aneurysm-related morbidity in the absence of endoleak at 1 month and 1 year. EVAR surveillance thus needs a CT scan follow-up at intervals mentioned to provide optimal EVAR results.

Conclusions

Endovascular repair of aortic aneurysm is a safe treatment option for patients with symptomatic AAA and asymptomatic AAA larger than 5.5 cm. EVAR offers the advantage of lower perioperative morbidity and mortality, shorter length of stay in the hospital, and early mobilization compared with open surgical repair. The increased cost of the device, surveillance, early and late complications, and secondary interventions should be considered in all patients undergoing EVAR. Lifelong surveillance with periodic CT scans can identify and treat late complications.

The decision between open surgical repairs versus EVAR for an AAA must be made by a cardiovascular team in a nonbiased manner. The patient and family member should be educated on the natural history, risk of rupture, mortality, and morbidity of each procedure in a detailed fashion to assist them in the decision-making process. Patient selection for EVAR based on the age, comorbidities, AAA anatomy suitability in terms of device IFU, experience of the implantation team, hospital experience, and hospital capacity to perform and follow-up are pivotal in providing optimal outcomes. EVAR should be performed at centers that have demonstrated an in-hospital mortality rate of less than 3% and primary conversion to open surgical repair rate of less than 2% for elective cases.

THORACIC ENDOVASCULAR AORTIC REPAIR

Background

Thoracic endovascular aortic repair was first performed by Dake et al.¹²¹ in 1992 at Stanford University Medical School. The early devices were composed of stainless steel stents with fabric Dacron material sutured as sleeve and delivered via 24-Fr sheath delivery systems. TEVAR is the preferred choice to treat thoracic aortic aneurysms

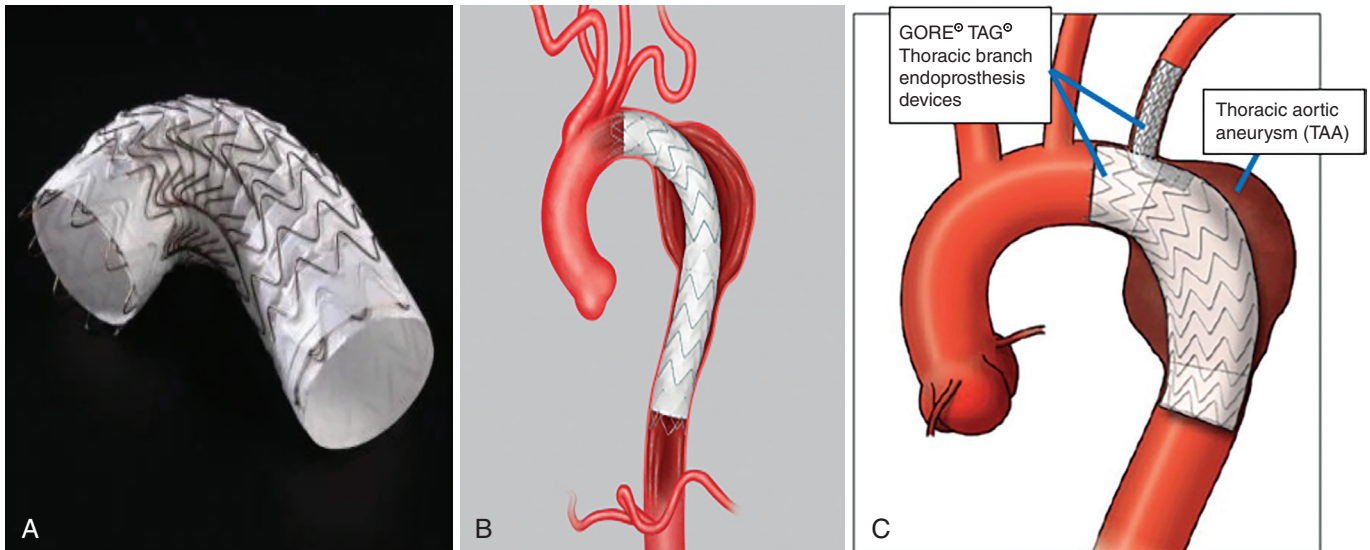


FIGURE 23.24 Thoracic endovascular aortic repair (TEVAR) device approved by the Food and Drug Administration. **A**, Gore confirmable Thoracic graft. **B**, Zenith Alpha Thoracic Endovascular Graft. **C**, GORE TAG Thoracic Branch Endoprosthesis (W.L. Gore and Associates).

(TAAs) compared with open repair because of reduced perioperative mortality and morbidity rates.¹²² TEVAR was originally developed to treat patients with TAAs; however, other pathologies such as aortic transection, dissection, intramural hematoma, and penetrating ulcer are now also being treated.¹²³ The advances in technology have enabled the low-profile devices with options to preserve flow into the aortic branches such as the subclavian artery.

Devices

Four devices are FDA approved for treatment of descending thoracic aorta aneurysms (DTAAs) (Figures 23.24 to 23.28):

1. Medtronic Talent, Valiant, Captiva, and Valiant Navion (Medtronic)
2. Gore TAG device (W.L. Gore and Associates)
3. Cook Zenith Tx1 and Tx2 and alpha thoracic endografts (Cook Medical)
4. Relay pro thoracic stent graft with non-bare-metal stent system

Indications for Thoracic Endovascular Aortic Repair

Indications for TEVAR include all symptomatic DTAAs and asymptomatic DTAAs that are twice the size of the adjacent aorta or larger than 6 cm. There must be sufficient landing zones with normal aortic dimension for the stent graft to provide adequate apposition to aortic walls.

The emerging indications for other aortic pathology are dissection involving the arch vessel, coarctation, aortic penetrating ulcers, and pseudoaneurysms.¹²⁴ Mycotic thoracic aneurysms can be treated temporarily with TEVAR; however, open surgery is still required in many cases¹²⁵ (Table 23.5).

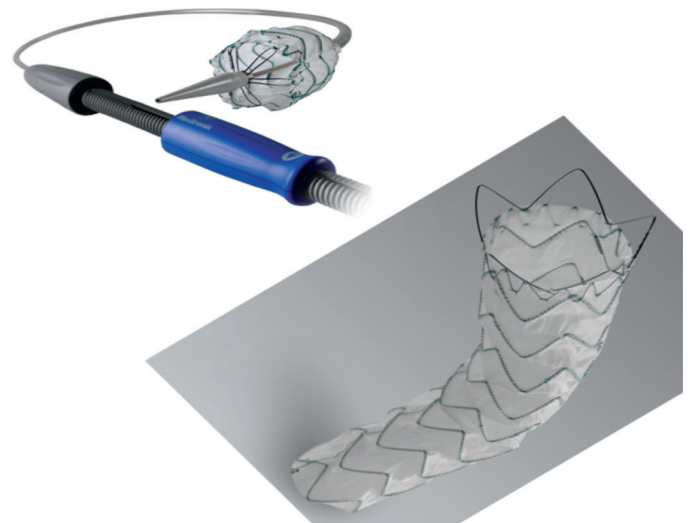


FIGURE 23.25 The Medtronic Talent device, a thoracic endovascular aortic repair device approved by the Food and Drug Administration.

Clinical Data for Thoracic Endovascular Aortic Repair

Early Experience

Dake and colleagues¹²¹ reported on the safety, feasibility, and effectiveness of TEVAR in 13 patients over a 2-year period. The aortic pathology that was treated included atherosclerotic aneurysm, aortic dissections, anastomotic aneurysm, and pseudoaneurysms with a mean diameter of 6.1 cm. The procedure was successful in all patients with complete thrombosis of the aneurysm around the graft in 12 patients, and 2 patients needed additional stent grafts. There were no deaths, paraplegia, stroke, distal embolization, or infection at 1-year follow-up.

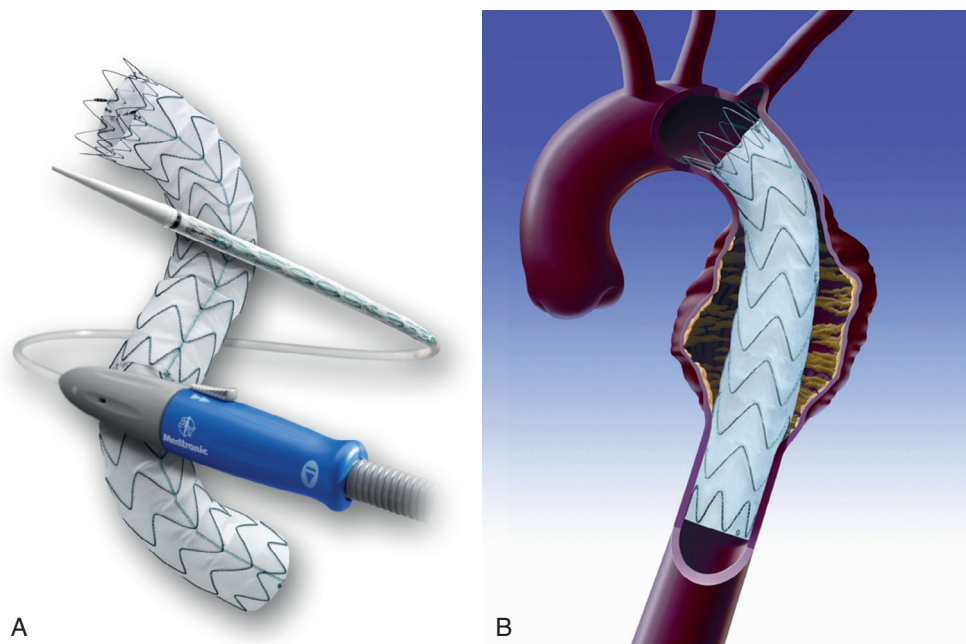


FIGURE 23.26 A and B, The Medtronic Valiant device, a thoracic endovascular aortic repair (TEVAR) device approved by the Food and Drug Administration.

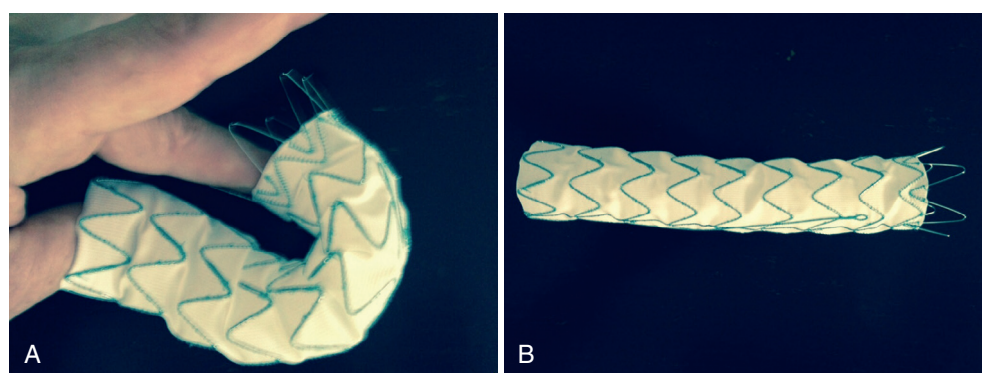


FIGURE 23.27 A and B, Relay thoracic device. (Bolton Medical). Thoracic endovascular aortic repair device approved by the Food and Drug Administration.

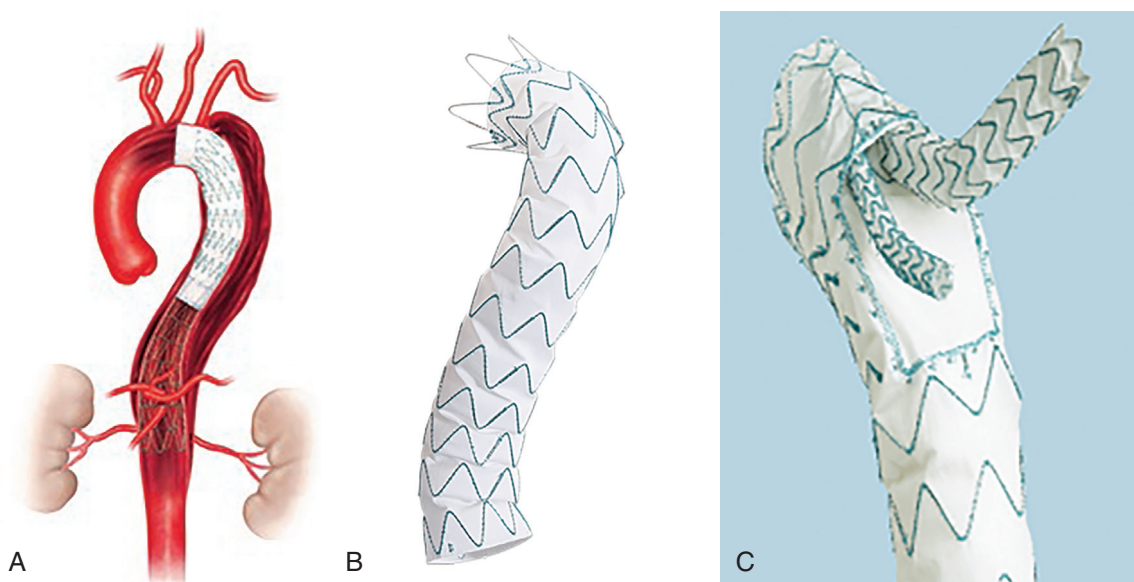


FIGURE 23.28 A, Cook Zenith Dissection Endovascular Stent. B, Relay Pro Terumo Thoracic graft. C, RelayBrand Thoracic Stent-Graft System (Cook Medical).

TABLE 23.5 Clinical Indications for Thoracic Endovascular Aortic Repair

Symptomatic	Descending thoracic aortic aneurysm, type B dissection, thoracic aortic transection, and pseudoaneurysm
Asymptomatic	Thoracoabdominal aneurysm >6.0 cm
	Rapid growth of 0.5 cm in 6 mo
	Type B dissection, thoracic aortic transection, and pseudoaneurysm

Aneurysmal Disease

Gore TAG investigators reported the results of a multicenter trial comparing the endovascular versus open surgical repair of DTAA.¹²⁶ A total of 140 patients from 17 sites received Gore TAG thoracic endografts (W.L. Gore and Associates). The perioperative mortality rate in the TEVAR versus open surgical group was 2.1% versus 11.7% ($P < .01$). At 30 days, there was a lower incidence of complications in the TEVAR group versus the open surgical group: respiratory failure (4% vs 20%), spinal cord ischemia (4% vs 14%), and renal insufficiency (1% vs 13%). The mean lengths of ICU stay and hospital stay were shorter in the TEVAR group. The endovascular group did have higher incidences of peripheral vascular complications, reinterventions, and endoleak of 6% and 9% at 1 and 2 years. There was no difference in mortality rates at 2 years between the two groups.

VALOR II (evaluation of the clinical performance of the valiant thoracic stent graft system in the treatment of DTAA of degenerative etiology in subjects who are candidates for endovascular repair) investigators performed a nonrandomized, prospective trial at 24 clinical sites and enrolled 160 patients.^{122,127} The outcomes of VALOR II were compared with VALOR (evaluation of the Medtronic vascular talent thoracic stent graft system for the treatment of TAA), which had 195 patients enrolled with similar enrollment criteria. TEVAR was successful in 96.3% of the patients, and at 30 days, the perioperative mortality rate was 3.1%, and major adverse events were seen in 38.1%, paraplegia in 0.6%, paraparesis in 1.9%, and stroke in 2.5% of patients. At 1 year, the aneurysm-related mortality rate was 4%, graft migration was seen in 2.9%, and endoleak was seen in 13% of patients. In addition, at 1 year, there were no ruptures, loss of stent graft patency, or conversion to open surgery.

A prospective international nonrandomized nonblinded trial enrolled 110 patients with TAAA (Thoracoabdominal aortic aneurysm) and penetrating atherosclerotic ulcers. A total of 82.7% of the patients were treated with Relay Pro thoracic endograft non-bare-stent configuration. The study was conducted across multiple centers in the United States and Japan from 2017 to 2019. The technical success rate was 100%, and the 30-day composite major adverse event rate was 6.4% (95% upper CI, 11.6%; $P = .0002$): 2 strokes, 2 cases of procedural blood loss greater than 1 L requiring transfusion, 2 paralysis events, and 1 renal failure. Nine patients had 11 events (1 aneurysm expansion, 6 secondary interventions, 4 types, 1 endoleak). There were no device fractures, migration, or loss of graft patency.¹²⁸

The Conformable Gore TAG Stent Graft for TAAA

The SURPASS registry was created to evaluate the performance of conformable Gore TAG stent grafts with an active

control system in patients undergoing TEVAR for TAAA. The registry was a single-arm, observational, postmarket, international prospective study involving 127 patients with TAAA, including ruptured aneurysms. The technical success rate was 87.6%, the stent graft was repositioned in 62% of cases, and the angulation feature was used in 50% of cases. There was no device compression, bird-beak configuration, graft occlusion, or fracture. At 30 days, there were three aorta-related deaths and three other deaths at 12 months. The deaths were caused by retrograde type A dissection, paraplegia, bowel ischemia, sepsis, aneurysm rupture after aortoesophageal fistula, and multiorgan dysfunction, and three endoleaks required intervention.¹²⁹

A prospective nonrandomized, multicenter study was conducted in Europe, Asia, and the United States using the Cook Zenith Alpha thoracic stent graft for TAAA or penetrating ulcers. A total of 110 patients were enrolled in the study. The device could not be implanted in 2 patients. There were no 30-day deaths; five deaths occurred before 1 year, resulting in 95% freedom from all-cause mortality and a 99% freedom from TAAA-related mortality. Type I endoleak was noted in 4 patients, type III endoleak in 2 patients, and aneurysm growth in 4 patients. At 1 year, there were 5 patients with stroke. No aortic rupture, paraplegia, paralysis, or permanent spinal cord injury was noted before 1 year.¹³⁰

Type B Aortic Dissection

Devices approved by the FDA are as follows:

1. The Zenith Dissection Endovascular system consisting of proximal stent graft component and distal bare stent. The FDA has approved the device for type B dissections of the descending aorta.
2. Medtronic Talent, Valiant, Captiva, and Valiant Navion (Medtronic)
3. Gore TAG device (W.L. Gore and Associates)

Acute aortic dissection is associated with considerable mortality and morbidity rates irrespective of surgical approach or medical management.¹³¹ Dake et al.¹²¹ studied the safety, effectiveness, and feasibility of TEVAR in patients with acute aortic dissections. A total of 19 patients were included: 4 patients with type A dissections and 15 patients with type B dissections of the descending thoracic aorta. Dissections involved aortic branches, and 7 patients had symptomatic compromise of branch vessels. The procedure was successful in all patients with complete and partial thrombosis of the false lumen in 15 and 4 patients, respectively. There were 3 deaths at 1 month and none at 13 months of follow-up.

Investigation of stent grafts in patients with type B aortic dissection INvestigation of STEnt Grafts in Aortic Dissection (INSTEAD) trial (INSTEAD-XL) evaluated a total of 140 patients with type B aortic dissection.¹³² A total of 72 patients previously randomized to medical treatment were enrolled

to TEVAR versus medical treatment alone for 68 patients. The risks of aorta-specific death (6.9% vs 19.3%; $P = .04$), all-cause mortality (11.1% vs 19.3%; $P = .13$), and disease progression (27.5% vs 46.1%; $P = .04$) were noted to be lower in the TEVAR group than in the medically treated patients at 5 years. TEVAR was associated with false lumen thrombosis in 90.6% of patients. In the United States, the Study of Thoracic Aortic Type B Dissection Using EndoLuminal REpair (STABLE) trial is examining TEVAR for uncomplicated dissections using the COOK (Cook Medical) thoracic endovascular stent graft.

Since the FDA approval for use of stent grafts for TEVAR in 2005, the number of cases with endograft implants for thoracic disease has increased exponentially. Physician-modified novel techniques such as carotid-to-subclavian bypass and graft fenestration have facilitated TEVAR in these complex cases.¹³³⁻¹³⁶

A meta-analysis of patients who had traumatic thoracic aortic transections by Tang et al.¹³⁷ analyzed 699 procedures published in 33 articles. TEVAR was performed in 370 patients, and 329 patients had open surgical repair. There was no difference in technical success rate between the two groups. The mortality rate was significantly lower in the TEVAR group (7.6% vs 15.2%; $P = .0076$), as were rates of stroke (0.85% vs 5.3%; $P = .0028$) and paraplegia (0% vs 5.6%; $P < .001$). The peripheral vascular complications, such as iliac artery injury, were high in the endovascular group.

Results of a multicenter, prospective trial of thoracic endovascular aortic repair for blunt thoracic aortic injury. The aim of the Clinical PeRformance of the Valiant Thoracic Stent Graft with the Captivia Delivery System for the Endovascular trEatment of Blunt Thoracic Aortic Injuries (RESCUE) trial was a multicenter, nonrandomized prospective trial conducted at 20 centers.¹³⁸ A total of 50 patients with blunt thoracic injury who underwent TEVAR were enrolled and followed for 5 years. The procedure was successful in all patients, and the 30-day mortality rate was 8%. The nonfatal adverse outcomes related to TEVAR were seen in 12% of patients. There were no events of spinal cord injury or cerebrovascular accidents, and no patient required conversion to open surgical repair.

Ruptured Thoracic Aortic Aneurysm

Gopaladas and colleagues¹³⁹ identified 923 patients who had undergone repair for ruptured TAA. Among these patients, 364 had TEVAR, and 559 underwent open surgical repair. Patients who underwent TEVAR were older and had higher comorbidities compared with open repair patients. The short-term outcomes of mortality, complications, and failure to rescue were similar between the two groups. TEVAR patients did have a greater chance of routine discharge. The smaller the size of the hospital was a predictor of complications, mortality, and failure to rescue in the open group compared with TEVAR. The study concluded that TEVAR may be a viable alternative to open repair in small-size hospitals where surgical expertise may be lacking for ruptured TAAs.

Endovascular Technique for Thoracic Endovascular Aortic Repair

Imaging for Thoracic Endovascular Aortic Repair

A 0.9- to 3-mm-slice CT scan with contrast that includes the chest, abdomen, and pelvis is pivotal in case planning for TEVAR. A 3D reconstruction of images is desirable to evaluate the aortoiliac pathology. MRA, conventional angiography, and IVUS are all acceptable imaging modalities and can be complementary. A thorough evaluation of iliac dimensions for suitability of large-bore access should be performed at baseline.

Aortic Arch Anatomy

Anatomic knowledge of the five zones in the arch of the aorta that can help in preplanning a successful TEVAR case is as follows (Figure 23.29):

- Zone 0: area proximal to the innominate artery
- Zone 1: area between the innominate artery and the left common carotid artery
- Zone 2: area between the left common carotid artery and left subclavian artery



FIGURE 23.29 A and B, Thoracic endovascular aortic repair for pseudoaneurysm in a patient with previous coarctation repair.

- Zone 3: area between the left subclavian artery and distal aorta at 2 cm
- Zone 4: area of the thoracic aorta more than 2 cm from the left subclavian artery

Aortic Arch Vessel Revascularization and Stent Graft Coverage

The aortic arch vessels, especially the left subclavian and left common carotid arteries, may need to be covered by the graft if the proximal landing zone is less than 2 cm to achieve an adequate seal. Anatomic knowledge of the cerebral vessels to determine the dominant vertebral artery and circle of Willis is essential before intentional left subclavian artery coverage with a stent graft. The options include carotid-to-left subclavian artery bypass, carotid-to-carotid artery bypass, or arch vessel debranching. The most common arch vessel involved is the left subclavian artery, and a left subclavian-to-carotid artery bypass is recommended for dominant left vertebral artery, patients with left internal mammary artery (LIMA) to left anterior descending artery bypass, direct origin of the left vertebral artery from aortic arch, and a patent left upper extremity arteriovenous dialysis fistula.

Physician-modified TEVAR can be performed wherein the graft is intentionally placed across the subclavian artery, and a laser-assisted fenestration of the graft is performed via the brachial artery. The origin of the left subclavian artery can be stented to preserve flow to the left arm, LIMA, and left vertebral artery.

Food and Drug Administration-Approved Grafts for Aortic Arch Vessel Revascularization

The Gore TAG thoracic branch endoprosthesis for treatment of proximal descending TAAs (zone 2). Thirty-one patients were enrolled from six centers in a nonrandomized prospective investigational device exemption trial of a single branched aortic endograft for management of TAAA that involved the distal arch. The unique branch endoprosthesis allows graft placement proximal to the subclavian artery, and the single side branch allows perfusion of the subclavian artery. The device was implanted in 100% of patients, and at 1 month, there was 100% patency of the side branch, and freedom from endoleak was noted in 96.7%, with no death or paraplegia. One patient had a procedure-related stroke. At 1 year, 5 patients died unrelated to the device or procedure. One thoracic reintervention was performed without any open repair conversion. At 6 months, 1 patient was noted to have an asymptomatic loss of side branch graft patency noted on a CT scan. At 1 year, 5 patients had endoleaks.¹³²

Spinal Drainage

Indications for pre-TEVAR cerebrospinal fluid (CSF) drainage include the need for extensive coverage of the descending thoracic aorta, multiple pieces of endovascular graft, previous AAA repair, coverage of the left subclavian artery, and aortic dissection with visceral or lower extremity malperfusion. Pre-TEVAR CSF drainage and monitoring for 24 to 48 hours can reduce the risk of paraplegia and improve mortality.¹⁴⁰

Vascular Access

Patients undergoing TEVAR should have suitable iliac dimensions to accommodate large-bore sheaths and grafts. If the CFA has atherosclerosis and calcification, it warrants a femoral cut down rather than a percutaneous approach. If the EIA demonstrates dense calcification, stenosis, small caliber, and tortuosity, then iliac conduits may be beneficial.

Perioperative Risk

A perioperative risk factor assessment can be beneficial in reducing the risk of perioperative cardiovascular events. A multidisciplinary approach to patient care involving endovascular operators, vascular surgery, cardiothoracic surgery, and anesthesia should be used to optimize clinical outcomes.

Anesthesia

General anesthesia, spinal, and MAC can be used for TEVAR, based on the cardiopulmonary status.

Operating Theater

Thoracic endovascular aortic repair cases should ideally be performed in large hybrid endovascular suites that have fixed fluoroscopy imaging. The imaging system should have a large screen image intensifier with digital subtraction, road mapping, and fluoroscopy save options. The air exchange in the room should not only suffice for a femoral cutdown but also for iliac artery repair or aorta exposure and control if needed. The hybrid room should be large enough for endovascular, surgical, and anesthesia equipment and personnel. Ceiling-mounted digital monitors for continuous vital signs monitoring are optimal.

Contraindications

Patient

The contraindications are TEVAR for an elective TAA patient with a life expectancy of fewer than six months Active infection or sepsis Infected aneurysm.

Aortic Arch and Distal Seal Zone

In patients with TAA with significant thrombus, tortuosity, and calcification, the graft delivery may be impeded, and the proximal seal may be affected. Distal aorta dimensions at the landing zone that are too large may not allow an adequate distal seal.

Iliac Access

A small-caliber iliac artery with calcification and severe atherosclerosis poses a risk for rupture and prevents graft delivery.

Aortic Branches

If the aortic branches are involved, they may prevent adequate perfusion to visceral organs and cerebral vessels.

Complications

Vascular access complications during TEVAR include bleeding, hematoma, a retroperitoneal bleed, and infection. The large-bore sheaths for TEVAR can pose a risk of iliac rupture. Inadvertent coverage of arch vessels during TEVAR can lead to myocardial infarction, endoleak, stroke, and death.



Step-by-Step Deployment of Thoracic Endovascular Aortic Repair Grafts

1. General, MAC, or epidural anesthesia is administered.
2. The CFA cutdown or Preclose ProGlide (Abbott Laboratories) is achieved to accommodate large-bore thoracic stent grafts.
3. Anticoagulation with heparin is preferred to achieve an ACT of greater than 150 seconds; in patients with a heparin allergy, bivalirudin may be used.
4. A stiff 0.035-inch wire, such as a Lunderquist wire (Cook Medical), is placed with a catheter support across the aortic arch with the curved wire tip in the ascending aorta close to the aortic root.
5. A contralateral femoral or radial access is obtained, and a 6-Fr sheath with a pigtail catheter is placed in the aortic arch. This access aids in pre- and post-TEVAR imaging and IVUS if needed.
6. The device or sheath is placed over the 0.035-inch wire, and all device advancements, especially across the iliac arteries, must be visualized under fluoroscopy.
7. The tip of the TEVAR graft is placed at the proximal end of the seal zone. To minimize device movement with the heartbeat, cardiac arrest can be achieved with adenosine injection or right heart pacing at 160 to 180 beats/min. A systolic blood pressure less than 100 mm Hg can aid in precise graft deployment.
8. The postdilation is performed with a molding balloon at the proximal and distal seal zones.
9. The pigtail catheter is withdrawn over a wire, and the graft is cannulated with the pigtail catheter into the ascending aorta.
10. A final angiogram is performed to evaluate for exclusion of the aneurysm, endoleak, and complications, such as perforation, dissection, or branch vessel closure.
11. Vascular access management with closure of the cutdown or approximation of the Preclose sutures is performed.

Postimplant Care and Discharge

If a spinal drain is used, patients are observed for 48 to 72 hours. If the patient is stable, the drain is clamped and subsequently removed. If no spinal drain was used and the patient is stable, TEVAR patients can be discharged at 24 to 48 hours.

Surveillance

Patients should be evaluated at 1 week for a femoral access site check for a hematoma, seroma, and suture removal (if a cutdown had been performed). At 30 days, a CT scan with contrast should be performed to evaluate the aneurysm for shrinkage and endoleaks. If there is no endoleak and no further increase in size, the CT scan should be repeated at 6 months and at 1 year thereafter.

Case 4

A 48-year-old male patient was seen for back pain with a history of repair of coarctation at age 9 months and 9 years. The patient also had plain old balloon angioplasty of the coarctation of the aorta at age 18 years. CTA of the chest, abdomen, and pelvis showed an aortic pseudoaneurysm measuring 6 cm of the descending aorta distal to the

left subclavian artery. The proximal landing zone measured 1.5 cm. A left subclavian artery-to-carotid bypass was performed. TEVAR was performed with percutaneous access using a Medtronic CAPTIVA to exclude the pseudoaneurysm. The patient had spinal drainage for 48 hours and was discharged home at 72 hours after an uneventful hospital course (see [Figure 23.29](#)).

Case 5

This case included an ascending aorta pseudoaneurysm treated with thoracic stent graft. A 72-year-old male patient underwent elective open mitral valve repair with neochordal implantation to the P2 segment of the posterior mitral leaflet and ring annuloplasty with a 31-mm Medtronic Duran Ancore annuloplasty band. The repair was complicated by an iatrogenic ascending aortic dissection initially treated by replacing the ascending aorta with a 24-mm Hemashield Dacron graft. After surgery, a 30-day follow-up CT scan demonstrated a small anastomotic pseudoaneurysm. On 21-month follow-up, the CT scan showed progression of the pseudoaneurysm, with a now 5-cm ascending aortic pseudoaneurysm originating from the lesser aortic curvature at the proximal Dacron graft anastomosis ([Figures 23.30](#)). Given the patient's advanced medical comorbidities (heart failure with reduced ejection fraction, chronic obstructive pulmonary disease with as-needed oxygen, atrial fibrillation requiring anticoagulation, frailty, and prior sternotomy), a heart team multidisciplinary discussion was held. The consensus was repairing with an endovascular approach.

On imaging review, the ascending aortic anatomy evaluated with a gated CT scan demonstrated the origin of pseudoaneurysm 30 mm above the coronary origin and 24 mm above the sinotubular junction. The innominate artery origin was 20 mm above the distal Dacron graft anastomosis. These dimensions ensured preoperatively that adequate flow to the arch vessels and coronary arteries could be achieved with a complete repair.

The patient was placed under GA in the angiography laboratory. Ultrasound-guided cannulation of the bilateral common femoral arteries and the left femoral vein was performed. The right femoral access was prepped for extensive bore sheath access with preclosure using two Abbott Perclose ProGlide devices, and a single Perclose ProGlide was deployed within the left. IVUS (0.035 Philips PV) was then used from the left 8-Fr sheath ([Figure 23.31](#)), and nonselective aortic angiography was obtained. Temporary right ventricular pacing was achieved through the venous cannulation site. The patient was systemically heparinized, and the 24-Fr Gore DrySeal sheath was advanced. A Cook Lunderquist wire was exchanged; however, adequate support still needed to be achieved, and a Cook Lunderquist Double Curve guidewire was exchanged. The Conformable GORE TAG with active control system (37-mm × 10-cm) device was deployed with predeployment subtraction imaging and active temporary ventricular pacing. Postdeployment IVUS assessment was performed, and a completion angiogram was obtained. The wires and sheaths were decannulated. Hemostasis was achieved within each access site with a combination of closure devices, Monocryl cutaneous sutures, and direct pressure. The patient was uneventfully awakened from GA.

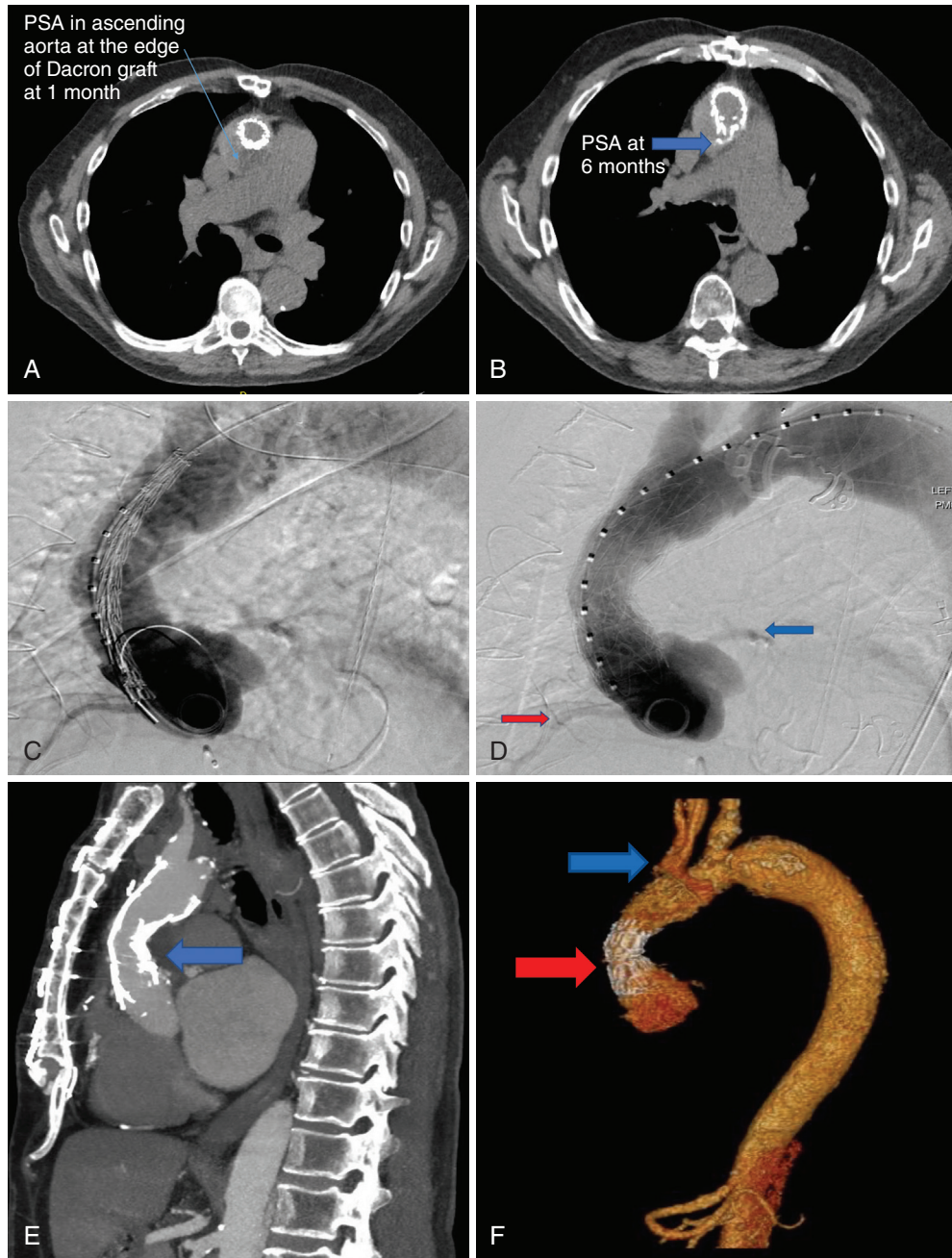


FIGURE 23.30 Ascending aorta pseudoaneurysm (PSA) treated with thoracic stent graft. **A** and **B**, A 79-year-old man after mitral valve repair was noted to have focal dissection of ascending aorta at the site of arterial cannulation and was treated with Dacron graft. At 1 and 6 months, ascending aorta PSA was noted at the edge of the Dacron graft. **C** and **D**, Thoracic endovascular aortic repair stent graft placement in the ascending aorta across the PSA. **C**, Angiogram shows the predeployed Gore graft. **D**, Postdeployment of the Gore graft with a nonobstructed left main coronary artery (blue arrow) and right coronary artery (red arrow). **E** and **F**, Computed tomography angiography of the ascending aorta at 6-month follow-up.

At 30 days and 1 year, CT imaging showed a patent stent graft in the ascending aorta and resolution of the pseudoaneurysm. Clinically, the patient did well without any further sequelae. The stent graft has successfully excluded the pseudoaneurysm. The postprocedure angiogram and subsequent contrasted CT scans showed coverage of the pseudoaneurysm, patent innominate artery, and no residual endoleak. The coronary angiogram showed no obstruction to the left main or right coronary arteries.

Conclusions

Thoracic endovascular aortic repair can be safely performed with low morbidity and mortality for patients with symptomatic or asymptomatic TAA greater than 6 cm, aortic transection, and type B dissection. Other indications include a ruptured TAA, pseudoaneurysm, and penetrating ulcer. Patient selection, with special attention to vascular access and branch vessel involvement, can reduce complications. A multidisciplinary approach to evaluate TEVAR patients and follow-up can optimize outcomes.

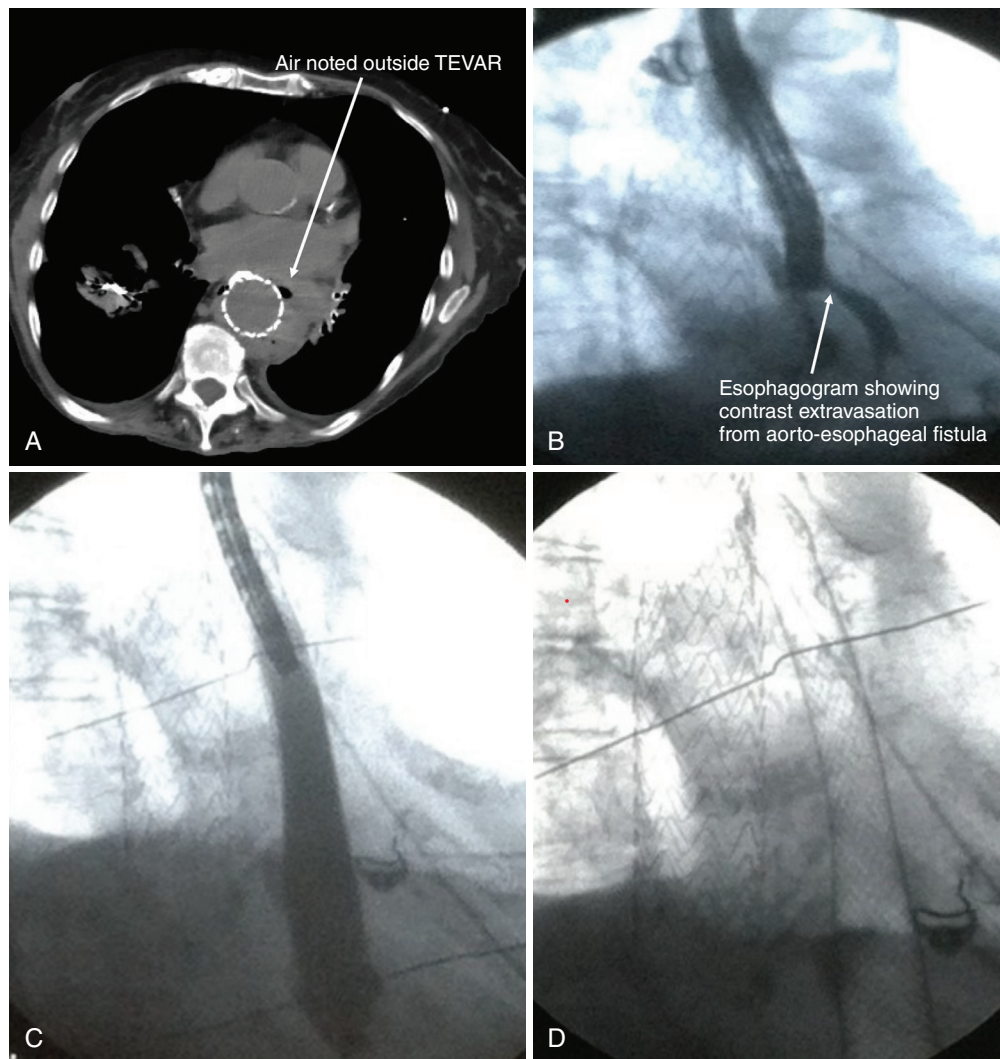


FIGURE 23.31 **A** and **B**, An 80-year-old patient with aorto-esophageal fistula presenting with hematemesis and epigastric pain treated with thoracic endovascular aortic repair (TEVAR) and esophageal stent. **A**, Esophagogram after esophageal stent shows no further contrast extravasation. **B**, Fluoroscopy shows the TEVAR stent graft and esophageal stent.

REFERENCES

- Johnston KW, Rutherford RB, Tilson MD, et al. Suggested standards for reporting on arterial aneurysms. Ad hoc Committee on Reporting Standards, Society for Vascular Surgery and North American Chapter, International Society for Cardiovascular Surgery. *J Vasc Surg.* 1991;13:452-458.
- Lederle FA, Johnson GR, Wilson SE, et al. Relationship of age, gender, race, and body size to infrarenal aortic diameter. *J Vasc Surg.* 1997;26:595-601.
- Singh K, Bønaa KH, Jacobsen BK, et al. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study. *Am J Epidemiol.* 2001;154:236-244.
- Reed D, Reed C, Stemmermann G, Hayashi T. Are aortic aneurysms caused by atherosclerosis? *Circulation.* 1992;85(1):205-211. doi:10.1161/01.cir.85.1.205.
- Galland RB, Simmons MJ, Torrie EP. Prevalence of abdominal aortic aneurysm in patients with occlusive peripheral vascular disease. *Br J Surg.* 1991;78:1259-1260.
- Lederle FA, Johnson GR, Wilson SE, et al. Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. *JAMA.* 2002;287:2968-2972.
- Cabellon S Jr, Moncrief CL, Pierre DR, et al. Incidence of abdominal aortic aneurysms in patients with atheromatous arterial disease. *Am J Surg.* 1983;146:575-576.
- Brady AR, Fowkes FG, Thompson SG, Powell JT. Aortic aneurysm diameter and risk of cardiovascular mortality. *Arterioscler Thromb Vasc Biol.* 2001;21(7):1203-1207.
- Nevitt MP, Ballard DJ, Hallett Jr, JW. Prognosis of abdominal aortic aneurysms. *N Engl J Med.* 1989;321(15):1009-1014.
- Brewster DC, Cronenwett JL, Hallett JW, Jr, et al. Guidelines for the treatment of abdominal aortic aneurysms. Report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. *J Vasc Surg.* 2003;37:1106-1117.
- Sakalihasan N, Limet R, Defawe OD. Abdominal aortic aneurysm. *Lancet.* 2005;365:1577-1589.
- Baxter BT, McGee GS, Flinn WR, McCarthy WJ, Pearce WH, Yao JS. Distal embolization as a presenting symptom of aortic aneurysms. *Am J Surg.* 1990;160(2):197-201.
- Singh K, Bønaa KH, Jacobsen BK, et al. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study: the Tromsø Study. *Am J Epidemiol.* 2001;154:236-244.
- Powell JT, Greenhalgh RM. Clinical practice. Small abdominal aortic aneurysms. *N Engl J Med.* 2003;348:1895-1901.
- Lederle FA, Johnson GR, Wilson SE, et al. Prevalence and associations of abdominal aortic aneurysm detected through screening. *Ann Intern Med.* 1997;126:441-449.
- Climent E, Benaiges D, Chillarón JJ, Roux JAF-L, Pedro-Botet J. Diabetes mellitus as a protective factor of abdominal aortic aneurysm: possible mechanisms. *Clin Invest Arterioscler.* 2018;30:181-187.
- Lederle FA, Johnson GR, Wilson SE, et al. The aneurysm detection and management study screening program: validation cohort and final results. Aneurysm Detection and Management Veterans Affairs cooperative study investigators. *Arch Intern Med.* 2000;160:1425-1430.
- Bengtsson H, Ekberg O, Aspelin P, et al. Ultrasound screening of the abdominal aorta in patients with intermittent claudication. *Eur J Vasc Surg.* 1989;3:497-502.
- Cabellon S Jr, Moncrief CL, Pierre DR, et al. Incidence of abdominal aortic aneurysms in patients with atheromatous arterial disease. *Am J Surg.* 1983;146:575-576.
- Diwan A, Sarkar R, Stanley JC, et al. Incidence of femoral and popliteal artery aneurysms in patients with abdominal aortic aneurysms. *J Vasc Surg.* 2000;31:863-869.
- Hinchliffe RJ, Macierewicz JA, Hopkinson BR. Endovascular repair of inflammatory abdominal aortic aneurysm. *J Endovasc Ther.* 2002;9:277.

22. Lindeman JH, Ashcroft BA, Beenakker JW, et al. Distinct defects in collagen microarchitecture underlie vessel-wall failure in advanced abdominal aneurysms and aneurysms in Marfan syndrome. *Proc Natl Acad Sci U S A*. 2010;107(2):862-865.
23. Taniyasu N, Tokunaga H. Multiple aortocaval fistulas associated with a ruptured abdominal aneurysm in a patient with Ehlers-Danlos syndrome. *Japan Circ J*. 1999;63(7):564-566.
24. Berchtold C, Eibl C, Seelig MH, et al. Endovascular treatment and complete regression of an infected abdominal aortic aneurysm. *J Endovasc Ther*. 2002;9:543-548.
25. Dieter RA Jr, Blum AS, Pozen TJ, et al. Endovascular repair of aortojejunal fistula. *Int Surg*. 2002;87:83-86.
26. Johansson G, Nydahl S, Olofsson P, et al. Survival in patients with abdominal aortic aneurysms. Comparison between operative and nonoperative management. *Eur J Vasc Surg*. 1990;4:497-502.
27. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. The UK Small Aneurysm Trial Participants. *Lancet*. 1998;352:1649-1655.
28. Gadowski GR, Pilcher DB, Ricci MA. Abdominal aortic aneurysm expansion rate: effect of size and beta-adrenergic blockade. *J Vasc Surg*. 1994;19:727-731.
29. Jones K, Brull D, Brown LC, et al. Interleukin-6 and the prognosis of abdominal aortic aneurysms. *Circulation*. 2001;103:2260-2265.
30. Hirsch AT, Haskal ZJ, Hertzner NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; Trans-Atlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation*. 2006;113:e463-e654.
31. Koole D, Zandvoort HJ, Schoneveld A, et al. Intraluminal abdominal aortic aneurysm thrombus is associated with disruption of wall integrity. *J Vasc Surg*. 2013;57:77-83.
32. Haller SJ, Crawford JD, Courchaine KM, et al. Intraluminal thrombus is associated with early rupture of abdominal aortic aneurysm. *J Vasc Surg*. 2018;67(4):1051-1058.
33. Chervu A, Clagett GP, Valentine RJ, et al. Role of physical examination in detection of abdominal aortic aneurysms. *Surgery*. 1995;117:454-457.
34. Aggarwal S, Qamar A, Sharma V, et al. Abdominal aortic aneurysm: a comprehensive review. *Exp Clin Cardiol*. 2011;16(1):11-15.
35. LaRoy LL, Cormier PJ, Matalon TA, et al. Imaging of abdominal aortic aneurysms. *AJR Am J Roentgenol*. 1989;152:785-792.
36. Petersen MJ, Cambria RP, Kaufman JA, et al. Magnetic resonance angiography in the preoperative evaluation of abdominal aortic aneurysms. *J Vasc Surg*. 1995;21:891-898.
37. Rydberg J, Kopecky KK, Johnson MS, et al. Endovascular repair of abdominal aortic aneurysms assessment with multislice CT. *AJR Am J Roentgenol*. 2001;177:607-614.
38. Marston WA, Ahlquist R, Johnson G Jr, et al. Misdiagnosis of ruptured abdominal aortic aneurysms. *J Vasc Surg*. 1992;16:17-22.
39. Akkersdijk GJ, van Bockel JH. Ruptured abdominal aortic aneurysm: initial misdiagnosis and the effect on treatment. *Eur J Surg*. 1998;164:29-34.
40. Baxter BT, McGee GS, Flinn WR, et al. Distal embolization as a presenting symptom of aortic aneurysms. *Am J Surg*. 1990;160:197-201.
41. Moll FL, Powell JT, Fraedrich G, et al; European Society for Vascular Surgery. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. *Eur J Vasc Endovasc Surg*. 2011;41(suppl 1):S1-S58.
42. Chaikof EL, Brewster DC, Dalman RL, et al; Society for Vascular Surgery. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. *J Vasc Surg*. 2009;50:S2-S49.
43. Brewster DC, Cronenwett JL, Hallett JW Jr, et al. Guidelines for the treatment of abdominal aortic aneurysms. Report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. *J Vasc Surg*. 2003;37:1106-1117.
44. Cronenwett JL, Sargent SK, Wall MH, et al. Variables that affect the expansion rate and outcome of small abdominal aortic aneurysms. *J Vasc Surg*. 1990;11:260-268.
45. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg*. 1991;5:491-499.
46. White GH, Yu W, May J, et al. A new nonstented balloon-expandable graft for straight or bifurcated endoluminal bypass. *J Endovasc Surg*. 1994;1:16-24.
47. Ivancev K, Malina M, Lindblad B, et al. Abdominal aortic aneurysms: experience with the Ivancev-Malmo endovascular system for aorto-monoiiliac stent-grafts. *J Endovasc Surg*. 1997;4:242-251.
48. Ohki T, Veith FJ, Sanchez LA, et al. Varying strategies and devices for endovascular repair of abdominal aortic aneurysms. *Semin Vasc Surg*. 1997;10:242-256.
49. Yusuf SW, Whitaker SC, Chuter TA, et al. Emergency endovascular repair of leaking aortic aneurysm. *Lancet*. 1994;344:1645.
50. May J, White GH, Yu W, et al. Current comparison of endoluminal versus open repair in the treatment of abdominal aortic aneurysms: analysis of 303 patients by the life table method. *J Vasc Surg*. 1998;27:213-221.
51. Schwarze ML, Shen Y, Hemmerich J, et al. Age-related trends in utilization and outcome of open and endovascular repair for abdominal aortic aneurysm in the United States, 2001–2006. *J Vasc Surg*. 2009;50:722-729.
52. Schermerhorn ML, Bensley RP, Giles KA, et al. Changes in abdominal aortic aneurysm rupture and short-term mortality, 1995–2008: a retrospective observational study. *Ann Surg*. 2012;256:651-658.
53. van Schaik TG, Yeung KK, Verhagen HJ, et al. Long-term survival and secondary procedures after open or endovascular repair of abdominal aortic aneurysms. *J Vasc Surg*. 2017;66(5):1379-1389.
54. Patel R, Sweeting MJ, Powell JT, Greenhalgh RM; EVAR trial investigators. Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. *Lancet*. 2016;388(10058):2366-2374.
55. The United Kingdom EVAR Trial Investigators. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomized controlled trial. *Lancet*. 2005;365(9478):2187-2192.
56. Lederle FA, Kyriakides TC, Stroupe KT, et al. Open versus endovascular repair of abdominal aortic aneurysm. *N Engl J Med*. 2019;380(22):2126-2135.
57. Antoniou GA, Antoniou SA, Torella F. Editor's choice – endovascular vs. open repair for abdominal aortic aneurysm: systematic review and meta-analysis of updated peri-operative and long term data of randomised controlled trials. *Eur J Vasc Endovasc Surg*. 2020;59(3):385-397.
58. Soares Ferreira R, Bastos Gonçalves F, Quintas A, Abreu R, Camacho N, Ferreira ME, Albuquerque e Castro J, Mota Capitão L. Planning, eva and followup without contrast in chronic kidney disease. *Angiol Cir Vasc [Internet]*. 2017 Dec. 30.
59. Piacentino F, Fontana F, Miceli C, et al. Nonenhanced MRI Planning for Endovascular Repair of Abdominal Aortic Aneurysms: Comparison With Contrast-Enhanced CT Angiography. *Vasc Endovascular Surg*. 2018;52:39-45.
60. Ultee KH, Soden PA, Zettervall SL, Darling J, Verhagen HJ, Schermerhorn ML. Conversion from endovascular to open abdominal aortic aneurysm repair. *J Vasc Surg*. 2016;64(1):76-82.
61. Elisha S, Nagelhout J, Heiner J, et al. Anesthesia case management for endovascular aortic aneurysm repair. *AANA J*. 2014;82(2):145-152.
62. Franz R, Hartman J, Wright M. Comparison of anesthesia technique on outcomes of endovascular repair of abdominal aortic aneurysms: a five-year review of monitored anesthesia care with local anesthesia vs. general or regional anesthesia. *J Cardiovasc Surg (Torino)*. 2011;52(4):567-577.
63. Armstrong RA, Squire YG, Rogers CA, Hinchliffe RJ, Mouton R. Type of anesthesia for endovascular abdominal aortic aneurysm repair. *J Cardiothorac Vasc Anesth*. 2019;33(2):462-471.
64. Rolls AE, Riga CV, Rudarakanchana N, et al. Planning for EVAR: the role of modern software [review]. *J Cardiovasc Surg (Torino)*. 2014;55(1):1-7.
65. Mann K, Sim I, Ali T, et al. Removing the need for crossmatched blood in elective EVAR. *Eur J Vasc Endovasc Surg*. 2012;43(3):282-285.
66. Mayer D, Rancic Z, Pfammatter T, et al. Logistic considerations for a successful institutional approach to the endovascular repair of ruptured abdominal aortic aneurysms. *Vascular*. 2010;18(2):64-70.
67. Maleux G, Koolen M, Heye S. Complications after endovascular aneurysm repair. *Semin Intervent Radiol*. 2009;26(1):3-9.
68. Hwang D, Kim J, Kim HK, Huh S. Suitability of the Aortic Neck Anatomy for Endovascular Aneurysm Repair in Korean Patients with Abdominal Aortic Aneurysm. *Vasc Specialist Int*. 2020;36(2):71-81.
69. Mathlouthi A, Khan MA, Al-Nouri O, Barleben A, Aburahma A, Malas MB. The correlation of aortic neck length to late outcomes following EVAR with the Ovation stent graft. *J Vasc Surg*. 2022;75(6):1890-1895.
70. Kritpracha B, Pigott JP, Russell TE, et al. Bell-bottom aortoiliac endografts: an alternative that preserves pelvic blood flow. *J Vasc Surg*. 2002;35:874-881.
71. Huang Y, Gloviczki P, Duncan AA, et al. Common iliac artery aneurysm: expansion rate and results of open surgical and endovascular repair. *J Vasc Surg*. 2008;47:1203-1211.
72. Antoniou GA, Nassef AH, Antoniou SA, et al. Endovascular treatment of isolated internal iliac artery aneurysms. *Vascular*. 2011;19:291-300.
73. Mehta M, Veith FJ, Ohki T, et al. Unilateral and bilateral hypogastric artery interruption during aortoiliac aneurysm repair in 154 patients: a relatively innocuous procedure. *J Vasc Surg*. 2001;33(suppl):S27-S32.
74. Geraghty PJ, Sanchez LA, Rubin BG, et al. Overt ischemic colitis after endovascular repair of aortoiliac aneurysms. *J Vasc Surg*. 2004;40:413-418.
75. Dadian N, Ohki T, Veith FJ, et al. Overt colon ischemia after endovascular aneurysm repair: the importance of microembolization as an etiology. *J Vasc Surg*. 2001;34:986-996.
76. Cynamon J, Lerer D, Veith FJ, et al. Hypogastric artery coil embolization prior to endoluminal repair of aneurysms and fistulas: buttock claudication, a recognized but possibly preventable complication. *J Vasc Interv Radiol*. 2000;11:573-577.
77. Lee WA, Nelson PR, Berceli SA, et al. Outcome after hypogastric artery bypass and embolization during endovascular aneurysm repair. *J Vasc Surg*. 2006;44:1162-1169.
78. Friedman SG, Wun H. Hypogastric preservation with Viabahn stent graft during endovascular aneurysm repair. *J Vasc Surg*. 2011;54:504-506.
79. Lobato AC. Sandwich technique for aortoiliac aneurysms extending to the internal iliac artery or isolated common/internal iliac artery aneurysms: a new endovascular approach to preserve pelvic circulation. *J Endovasc Ther*. 2011;18:106-111.
80. Ferrer C, De Crescenzo F, Coscarella C, Cao P. Early experience with the Excluder® iliac branch endoprosthesis. *J Cardiovasc Surg (Torino)*. 2014;55:679-683.

81. Schneider DB, Matsumura JS, Lee JT, Peterson BG, Chaer RA, Oderich GS. Prospective, multicenter study of endovascular repair of aortoiliac and iliac aneurysms using the Gore Iliac Branch Endoprosthesis. *J Vasc Surg.* 2017;66(3):775-785.
82. Franz RW, Ibrahim MT, Tanga CF, Epstein DA. Endovascular Treatment of Abdominal Aortic Aneurysm with Complete Iliac Occlusion: Case Series and Literature Review. *Int J Angiol.* 2017;26(4):259-263.
83. van Groenendaal L, Zeebregts CJ, Verhoeven EL, et al. External-to-internal iliac artery endografting for the exclusion of iliac artery aneurysms: an alternative technique for preservation of pelvic flow? *Catheter Cardiovasc Interv.* 2009;73:156-160.
84. Manunga JM, Glociczki P, Oderich GS, et al. Femoral artery calcification as a determinant of success for percutaneous access for endovascular abdominal aortic aneurysm repair. *J Vasc Surg.* 2013;58:1208-1212.
85. Torsello GB, Kasprzak B, Klenk E, et al. Endovascular suture versus cut-down for endovascular aneurysm repair: a prospective randomized pilot study. *J Vasc Surg.* 2003;38:78-82.
86. Fernandez JD, Craig JM, Garrett HE Jr, et al. Endovascular management of iliac rupture during endovascular aneurysm repair. *J Vasc Surg.* 2009;50(6):1293-1299.
87. Peterson BG, Matsumura JS. Creative options for large sheath access during aortic endografting. *J Vasc Interv Radiol.* 2008;19(6 suppl):S22-S26.
88. Lee A, Brown MP, Nelson PR, et al. Midterm outcomes of femoral arteries after percutaneous endovascular aortic repair using the Preclose technique. *J Vasc Surg.* 2008;47:919-923.
89. Lee WA, Brown MP, Nelson PR, et al. Total percutaneous access for endovascular aortic aneurysm repair ("Preclose" technique). *J Vasc Surg.* 2007;45:1095-1101.
90. Krajcer Z, Matos JM. Totally percutaneous endovascular abdominal aortic aneurysm repair: 30-day results from the independent access-site closure study of the PEVAR trial. *Tex Heart Inst J.* 2013;40(5):560-561.
91. Wood DA, Krajcer Z, Sathananthan J, et al; SAFE MANTA Study Investigators. Pivotal Clinical Study to Evaluate the Safety and Effectiveness of the MANTA Percutaneous Vascular Closure Device. *Circ Cardiovasc Interv.* 2019;12(7):e007258.
92. Eisenack M, Umscheid T, Tessarek J, et al. Percutaneous endovascular aortic aneurysm repair: a prospective evaluation of safety, efficiency, and risk factors. *J Endovasc Ther.* 2009;16:708-713.
93. Mousa AY, Campbell JE, Broce M, et al. Predictors of percutaneous access failure requiring open femoral surgical conversion during endovascular aortic aneurysm repair. *J Vasc Surg.* 2013;58:1213-1219.
94. Greenberg JL, Dorsey C, Dalman RL, et al. Long-term results after accessory renal artery coverage during endovascular aortic aneurysm repair. *J Vasc Surg.* 2012;56(2):291-296, discussion 296-297.
95. Chaudhuri A. Exclusion of an infrarenal AAA with coincident horseshoe kidney and renovascular anomalies is feasible using a standard stent-graft. *Eur J Vasc Endovasc Surg.* 2011;41(5):654-656.
96. Tan TW, Farber A. Percutaneous endovascular repair of abdominal aortic aneurysm with coexisting horseshoe kidney: technical aspects and review of the literature. *Int J Angiol.* 2011;20(4):247-250.
97. Carpenter JP, Baum RA, Barker CF, et al. Impact of exclusion criteria on patient selection for endovascular abdominal aortic aneurysm repair. *J Vasc Surg.* 2001;34:1050-1054.
98. Greenberg R, Eagleton M, Mastracci T. Branched endografts for thoracoabdominal aneurysms. *J Thorac Cardiovasc Surg.* 2010;140(6 suppl):S171-S178.
99. Zenith Fenestrated Study Investigators. Results of the United States multicenter prospective study evaluating the Zenith fenestrated endovascular graft for treatment of juxtarenal abdominal aortic aneurysms. *J Vasc Surg.* 2014;60(6):1420-1428.
100. Stavropoulos SW, Charagundla SR. Imaging techniques for detection and management of endoleaks after endovascular aortic aneurysm repair. *Radiology.* 2007;243:641-655.
101. White GH, Yu W, May J, et al. Endoleak as a complication of endoluminal grafting of abdominal aortic aneurysms: classification, incidence, diagnosis and management. *J Endovasc Surg.* 1997;4:152-168.
102. AbuRahma AF, Campbell JE, Mousa AY, et al. Clinical outcomes for hostile versus favorable aortic neck anatomy in endovascular aortic aneurysm repair using modular devices. *J Vasc Surg.* 2011;54(1):13-21.
103. Kim JK, Noll RE Jr, Tonnessen BH, et al. A technique for increased accuracy in the placement of the "giant" Palmaz stent for treatment of type IA endoleak after endovascular abdominal aortic aneurysm repair. *J Vasc Surg.* 2008;48:755-757.
104. Varcoe RL, Laird MP, Frawley JE. A novel alternative to open conversion for type I endoleak resulting in ruptured aneurysm. *Vasc Endovascular Surg.* 2008;42:391-393.
105. Jonker FH, Aruny J, Muhs BE. Management of type II endoleaks: preoperative versus post-operative versus expectant management. *Semin Vasc Surg.* 2009;22:165-171.
106. Burley CG, Kumar MH, Bhatti WA, Boyd C, Sales CM. Transcaval embolization as the preferred approach. *J Vasc Surg.* 2019;69(4):1309-1313.
107. Chuter TA, Faruqi RM, Sawhney R, et al. Endoleak after endovascular repair of abdominal aortic aneurysm. *J Vasc Surg.* 2001;34:98-105.
108. Naoki T, Tetsuji F, Yuji K, et al. Endotension following endovascular aneurysm repair. *Vasc Med.* 2008;13:305-331.
109. Ohki T, Ouriel K, Silveria PG, et al. Initial results of wireless pressure sensing for EVAR: the APEX trial—acute pressure measurement to confirm aneurysm sac exclusion. *J Vasc Surg.* 2007;45:236-242.
110. Carroccio A, Faries PL, Morrissey NJ, et al. Predicting iliac limb occlusions after bifurcated aortic stent grafting: anatomic and device-related causes. *J Vasc Surg.* 2002;36:679-684.
111. Parent FN III, Godziachvili V, Meier GH III, et al. Endograft limb occlusion and stenosis after ANCORE endovascular abdominal aneurysm repair. *J Vasc Surg.* 2002;35:686-690.
112. Powell A, Fox LA, Benenati JF, et al. Postoperative management: buttock claudication and limb thrombosis. *Tech Vasc Interv Radiol.* 2001;4:232-235.
113. Naoki T, Tetsuji F, Yuji K, et al. Endotension following endovascular aneurysm repair. *Vasc Med.* 2008;13:305-331.
114. Lin PH, Bush RL, Katzman JB, et al. Delayed aortic aneurysm enlargement due to endotension after endovascular abdominal aortic aneurysm repair. *J Vasc Surg.* 2003;38:840-842.
115. Ohki T, Ouriel K, Silveria PG, et al. Initial results of wireless pressure sensing for EVAR: the APEX trial—acute pressure measurement to confirm aneurysm sac exclusion. *J Vasc Surg.* 2007;45:236-242.
116. Carroccio A, Faries PL, Morrissey NJ, et al. Predicting iliac limb occlusions after bifurcated aortic stent grafting: anatomic and device-related causes. *J Vasc Surg.* 2002;36:679-684.
117. Noll RE Jr, Tonnessen BH, Mannava K, et al. Long-term follow-up cost after endovascular aneurysm repair. *J Vasc Surg.* 2007;46:9-15.
118. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med.* 2007;357:2277-2284.
119. Noll RE Jr, Tonnessen BH, Mannava K, et al. Long-term follow-up cost after endovascular aneurysm repair. *J Vasc Surg.* 2007;46:9-15.
120. Sternbergh WC 3rd, Greenberg RK, Chuter TA, et al. Redefining postoperative surveillance after endovascular aneurysm repair: recommendations based on 5-year follow-up in the US Zenith multicenter trial. *J Vasc Surg.* 2008;48:278-284.
121. Dake MD, Miller DC, Semba CP, et al. Transluminal placement of endovascular stent-grafts for the treatment of descending thoracic aortic aneurysms. *N Engl J Med.* 1994;331(26):1729-1734.
122. Bavaria JE, Appoo JJ, Makaroun MS, et al. Endovascular stent grafting versus open surgical repair of descending thoracic aortic aneurysms in low-risk patients: a multicenter comparative trial. *J Thorac Cardiovasc Surg.* 2007;133(2):369-377.
123. Dake MD, Kato N, Mitchell RS, et al. Endovascular stent-graft placement for the treatment of acute aortic dissection. *N Engl J Med.* 1999;340:1546-1552.
124. Dagenais F, Shetty R, Normand J-P, et al. Extended applications of thoracic aortic stent grafts. *Ann Thorac Surg.* 2006;82:567-572.
125. Vallejo N, Picardo NE, Bourke P, et al. The changing management of primary mycotic aortic aneurysms. *J Vasc Surg.* 2011;54(2):334-340.
126. Dake MD, Fischbein MP, Bavaria JE, et al. Evaluation of the Gore TAG thoracic branch endoprosthesis in the treatment of proximal descending thoracic aortic aneurysms. *J Vasc Surg.* 2021;74(5):1483-1490.
127. Fairman RM, Tucheck JM, Lee WA, et al. Pivotal results for the Medtronic Valiant Thoracic Stent Graft System in the VALOR II trial. *J Vasc Surg.* 2012;56(5):1222-1231.
128. Szeto WY, Vallabhajosyula P, Matsuda H, et al. One-year results with a low-profile endograft in subjects with thoracic aortic aneurysm and ulcer pathologies. *J Thorac Cardiovasc Surg.* 2022;163(5):1739-1750.
129. Torsello GF, Argiriou A, Stavroulakis K, et al. One-year results from the SURPASS observational registry of the CTAG stent-graft with the Active Control System. *J Endovasc Ther.* 2020;27(3):421-427.
130. Illig KA, Ohki T, Hughes GC, et al. One-year outcomes from the international multicenter study of the Zenith Alpha Thoracic Endovascular Graft for thoracic endovascular repair. *J Vasc Surg.* 2015;62(6):1485-1494.
131. Trimarchi S, Nienaber CA, Rampoldi V, et al. Role and results of surgery in acute type B aortic dissection: insights from the International Registry of Acute Aortic Dissection (IRAD). *Circulation.* 2006;114(1 suppl):I357-I364.
132. Nienaber CA, Kische S, Rousseau H, et al; INSTEAD-XL trial. Endovascular repair of type B aortic dissection: long-term results of the randomized investigation of stent grafts in aortic dissection trial. *Circ Cardiovasc Interv.* 2013;6(4):407-416.
133. Clough RE, Mani K, Lyons OT, et al. Endovascular treatment of acute aortic syndrome. *J Vasc Surg.* 2011;54(6):1580-1587.
134. Murad MH, Rizvi AZ, Malgor R, et al. Comparative effectiveness of the treatments for thoracic aortic transection. *J Vasc Surg.* 2011;53(1):193-199, e1-e21.
135. Mikhail P, Hess PJ Jr, Klodell CT, et al. Closure of type I endoleaks and landing zone preparation of the thoracic aorta. *Ann Thorac Surg.* 2008;85(2):e9-e11.
136. Patel PJ, Grande W, Hieb RA. Endovascular management of acute aortic syndromes. *Semin Intervent Radiol.* 2011;28(1):10-23.
137. Tang GL, Tehrani HY, Usman A, et al. Reduced mortality, paraplegia, and stroke with stent graft repair of blunt aortic transections: a modern meta-analysis. *J Vasc Surg.* 2008;47(3):671-675.
138. Khojenezhad A, Azizzadeh A, Donayre CE, et al. Results of a multicenter, prospective trial of thoracic endovascular aortic repair for blunt thoracic aortic injury (RESCUE trial). *J Vasc Surg.* 2013;57(4):899-905.
139. Gopaldas RR, Dao TK, LeMaire SA, et al. Endovascular versus open repair of ruptured descending thoracic aortic aneurysms: a nationwide risk-adjusted study of 923 patients. *J Thorac Cardiovasc Surg.* 2011;142(5):1010-1018.
140. Cheung AT, Weiss SJ, McGarvey ML, et al. Interventions for reversing delayed-onset postoperative paraplegia after thoracic aortic reconstruction. *Ann Thorac Surg.* 2002;74(2):413-419, discussion 420-421.



24 Carotid And Vertebral Intervention

WILLIAM A. GRAY

CAROTID INTERVENTION, 441
The Data, 441

The Procedure, 448
CONCLUSIONS, 459

CAROTID INTERVENTION

The Data

When discussing the clinical data for outcomes in carotid artery stenting (CAS), there are several important outcomes to be detailed: periprocedural (30 day) safety, which is composed of death, all stroke, and myocardial infarction (MI); 1-year stroke prevention efficacy composed of ipsilateral stroke rates from 30 to 365 days; and durability, which is measured by restenosis greater than 70% to 80% in severity or the need for repeat revascularization. All of these will necessarily be measured against carotid artery endarterectomy (CEA), the standard of care for carotid bifurcation disease requiring intervention.

Although the first reports of endovascular approaches to carotid artery disease were used in nonatherosclerotic lesions and date back to the early 1980s,¹ the use of stents to augment angioplasty results did not come into routine use until the mid-to-late 1990s. When studied in the first large-scale, multicenter CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study) started in 1995, balloon angioplasty was used alone in 75% of the trial participants randomized to an endovascular approach for symptomatic carotid disease, with the last 25% of this enrollment employing stent implantation.² The results of the UK-based CAVATAS suggested no short-term differences in safety and clinical efficacy between CEA and carotid angioplasty. But two important caveats to this conclusion are warranted. First, the restenosis rate in the angioplasty group was higher than in the CEA group likely related to the lack of a stent scaffold in the majority of cases. Second, although the results between groups were not different, the rates (~10%) of 30-day death and stroke were higher than the standards established by the NASCET (North American Symptomatic Carotid Endarterectomy Trial) for symptomatic lesions³—and not a good showing for either approach. Importantly, not only were stents not used in the majority of patients but embolic protection devices (EPDs) were also still not developed and therefore not used at all in CAVATAS, thus making these results largely irrelevant in today's era of "modern" CAS with standard EPD.

Although CAS with EPD was introduced around 1999, the full penetration of this technology was not realized in Europe (EU) until several years later and was more delayed in the United States. The earlier approval of the technology in Europe did not translate into a deep pool of experienced operators capable of contributing expertly to studies of CAS and CEA early in the decade when the EU trials were under way. In fact, of the three EU randomized trials, all in symptomatic patients, examining the relative safety and efficacy of these two treatments—EVA-3S (Endarterectomy Versus Stenting in patients with Symptomatic Severe carotid Stenosis), SPACE (Stent-Protected Angioplasty versus Carotid Endarterectomy), and ICSS (International Carotid Stenting Study)—two were severely confounded by gross CAS operator inexperience, both on an absolute basis and relative to the CEA trial surgeon experience, making the results highly problematic.^{4,6} Additionally, confounding all three of these studies was the failure to include or routinely measure MI as an endpoint despite ample data demonstrating that MI in the perioperative period has significant long-term mortality implications for the patient.⁷ Equally problematic, EPDs were not mandated in any of the studies from the outset, although after a significant number of strokes had already occurred with CAS in EVA-3S in the first approximately 80 patients, EPD was finally made standard.

As a result of these and other construct and conduct issues within these EU trials, many of which can be ascribed to their premature initiation in an underdeveloped and novel therapy, their results are both predictable and unfortunate in that they are not helpful in determining the place of CAS in symptomatic patient management today. The French EVA-3S study was the first to report its data in 2006 and had to be halted early after approximately 500 patients because of safety concerns in the CAS arm. The primary endpoint of 30-day death and stroke was 3.9% in the CEA arm and 9.6% in the CAS arm. The second trial to report was the German SPACE (2007) trial, which was also stopped early when a prespecified interim analysis at 1200 patients suggested the need for roughly another 1200 patients at the same event rates to reach a statistically meaningful endpoint, at which point the government funding agency withdrew support; nevertheless, there was no difference detected in the 30-day endpoint of death and

stroke between CEA and CAS, 6.3% versus 6.8%, respectively; EPDs were used only 27% of the time. The last to report was the UK-based ICSS trial, which reported an interim nonprimary endpoint in 2008 demonstrating more outcome events with CAS (8.5%) than CEA (5.2%) but that ultimately reported its 3-year primary endpoint of disabling stroke and death, demonstrating no differences between the two therapies.

The progression of study followed a different course in the United States than in Europe. After several reports of reasonable outcomes in CAS in high surgical risk patients using off-label devices, including tracheobronchial stents (which were used because they had delivery systems long enough to reach the carotid from the transfemoral route), device development including dedicated nitinol stents and EPDs got under way.^{8,9} Subsequently, the Food and Drug Administration (FDA) Investigational Device Exemption (IDE) approval process dictated that studies would need to be compared with CEA. Because the procedural safety profile of CAS using EPD had not been fully established,¹⁰ the comparator group was mandated to be patients who were deemed to require CEA but were at high risk for the operation by virtue of either anatomic or physiologic comorbidities. These conditions are listed in Table 24.1. The first US trial to use these inclusion criteria was the randomized SAPHIRE (Stenting and Angioplasty with

Protection in Patients at High Risk for Endarterectomy) study,¹¹ which tested the Precise carotid stent and the Angioguard filter EPD (Cordis/Johnson & Johnson). SAPHIRE turned out to be the only multicenter prospective examination of CEA in a high surgical risk cohort, which had largely been excluded from the landmark CEA trials such as the NASCET, ACAS (Asymptomatic Carotid Atherosclerosis Study), and ACST (Asymptomatic Carotid Surgery Trial). Unfortunately, the SAPHIRE trial did not go to completion because it did not enroll a patient in its last 6 months, thought likely to be because of the availability of other competitive nonrandomized IDE studies that guaranteed the interested participants would get CAS. These other single-arm studies used objective performance criteria (OPC) to compare the CAS outcomes with and were constructed from a literature review of CEA outcomes in high surgical risk patients in the various categories of surgical risk (e.g., lung disease, congestive heart failure, prior CEA). They then weighted contributions according to the actual percentage of each category enrolled in the specific trial. Although this may seem like an inexact science, in fact, the high-risk surgical arm of SAPHIRE had roughly the same 1-year outcomes that were modeled using the OPC method, which validated this approach; this method became the de facto standard for device trials in CAS for both IDE stent approval and 510(k) EPD clearance.

Although it was not enrolled to its targeted trial goal, the SAPHIRE study nevertheless randomized enough participants to demonstrate that in a mixed population of symptomatic and asymptomatic patients at high surgical risk for CEA, CAS was noninferior to CEA in the primary endpoint of 30-day death, stroke, and MI plus ipsilateral stroke and death to 1 year with trends favoring CAS.

The next high surgical risk population CAS study completed and reporting data was the ACCULINK for Revascularization of Carotids in High-Risk patients (ARChER) trial,¹² which tested the Acculink stent and Accunet EPD system (Abbott Vascular) and was the first single-arm study to compare to an OPC. The ARChER study's 30-day death, stroke, and MI plus ipsilateral stroke to 1 year rate was 8.3%, the upper limit of the 95% confidence interval (CI) of which was able to satisfy the OPC endpoint estimate of 14.4%. This study led to FDA approval for this carotid stent system, the first in the United States, in 2004. Thereafter, a series of single-arm studies led to FDA approval or clearance for a variety of stents and filters, respectively, which are listed in Table 24.2. It is noteworthy that no device tested for use in CAS in the United States has failed to establish safety and efficacy by FDA standards.

As a condition of approval for many of the early devices tested, the FDA mandated postmarket surveillance registries of approximately 1500 patients to assess for any rare or unanticipated device events not seen in the smaller pivotal studies, as well as the ability to transfer the technology into the more generalizable nontrial setting. These single-arm prospective multicenter studies, replete with independent procedural and 30-day neurologic assessment along with independent clinical event committees, were voluntarily extended by the device manufacturers

TABLE 24.1 High-Risk Factors for Carotid Artery Endarterectomy

HIGH-RISK CATEGORY Age (y)	CRITERIA Older than 80
Severe cardiac dysfunction	NYHA Class III/IV chronic heart failure LVEF <30% Open heart surgery within 6 wk MI within 4 wk NYHA Class III/IV angina Cardiac stress test result positive for ischemia
Severe renal dysfunction	ESRD on dialysis
Severe chronic lung disease	Chronic oxygen therapy $pO_2 \leq 60$ mm Hg Baseline hematocrit $\geq 50\%$ FEV_1 or DLCO $\leq 50\%$ of predicted
Anatomic comorbidities	Prior cervical radiation therapy Previous ipsilateral carotid endarterectomy C2 or higher carotid bifurcation Contralateral carotid occlusion Contralateral laryngeal nerve palsy Presence of a tracheostomy Common carotid artery lesion(s) below the clavicle

DLCO, Diffusing capacity of lung for carbon monoxide; FEV_1 , forced expiratory volume in 1 s; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; pO_2 , partial oxygen pressure.
From <http://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R77NCD.pdf>.

TABLE 24.2 Summary of US Investigational Device Exemption Carotid Artery Stenting Device Trials

IDE TRIAL	n (CAS)	YEAR OF FDA ACTION	STENT SYSTEM APPROVAL OR EPD 510(K) CLEARANCE	POSTMARKET SURVEILLANCE STUDY
ARCHeR	581	2004	Acculink PMA approval AccUNET 510(k) clearance	CAPTURE (<i>n</i> = 4225) CAPTURE (<i>n</i> = 6361) CHOICE (<i>n</i> = 19,000)
SECURITY	305	2005	Xact PMA approval Emboshield 510(k) clearance	EXACT (<i>n</i> = 2145) CHOICE
SAPPHIRE	565	2006	Precise PMA approval Angioguard 510(k) clearance	CASES-PMS (<i>n</i> = 1493) SAPPHIRE WW (<i>n</i> = 15,000)
CABERNET	488	2006	NexStent PMA approval FilterWire Carotid 510(k) clearance	None
CREATE	419	2006 2007	Protégé Carotid PMA approval SpiderFX Carotid 510(k) clearance	CREATE PAS (<i>n</i> = 3500)
MaVerIC	449	2007	Exponent PMA approval GuardWire Carotid 510(k) clearance	None
PROTECT	320	2008	Emboshield NAV6 510(k) clearance	CHOICE
BEACH	480	2008	Wallstent Carotid PMA approval FilterWire EX System clearance	CABANA (<i>n</i> = 1097)
EPIC	237	2008	Fibernet 510(k) clearance	None
EMBOLDEN	250	2009	GORE Embolic Filter clearance	None
EMPIRE	245	2009	Gore Flow Reversal 510(k) clearance	FREEDOM (planned <i>N</i> —5000)
ARMOUR	228	2009	Mo.Ma 510(k) clearance	None
CREST	1131	2011	Acculink PMA extension	CANOPY (planned <i>N</i> —1200)

ARCHeR, ACCULINK for Revascularization of Carotids in High-Risk patients; ARMOUR, Proximal Protection with the Mo.Ma Device During Carotid Stenting; BEACH, Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients; CABANA, Carotid Stenting Boston Scientific Surveillance Program; CABERNET, Carotid Revascularization Using the Boston Scientific FilterWire EX/EZ and the EndoTex NexStent; CANOPY, Carotid Artery Stenting Outcomes in the Standard Risk Population for Carotid Endarterectomy; CAPTURE, Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Unanticipated or Rare Events; CAS, carotid artery stenting; CHOICE, Carotid Stenting for High Surgical-Risk Patients; CREATE, Carotid Revascularization with ev3 Arterial Technology Evolution; CREATE PAS, Carotid Revascularization with ev3 Arterial Technology Evolution Post-Approval Study; CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; EMBOLDEN, GORE Embolic Filter in Carotid Stenting for High Risk Surgical Subjects; EMPIRE, Embolic Protection with Reverse Flow; EPD, embolic protection device; EPIC, Evaluating the Use of the FiberNet Embolic Protection System in Carotid Artery Stenting; EXACT, Emboshield and Xact; FDA, Food and Drug Administration; FREEDOM, GORE Flow Reversal System and GORE Embolic Filter Extension Study for the Ongoing Collection of Patient Outcomes; IDE, Investigational Device Exemption; MaVerIC, Medtronic AVE Self-expanding Carotid Stent System with distal protection in the treatment of Carotid stenosis; PMA, Pre-market approval; PMS, Post-market approval study; PROTECT, PROTECTed Carotid Artery Stenting in Subjects at High-Risk for Carotid Endarterectomy; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SAPPHIRE WW, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SECURITY, Registry Study to Evaluate the Neuroshield Bare Wire Cerebral Protection System and X-Act Stent in Patients at High Risk for Carotid Endarterectomy. From Gray WA, Verta P. The impact of regulatory approval and Medicare coverage on outcomes of carotid stenting. *Catheter Cardiovasc Interv*. 2014;83:1158-1166.

and have yielded high-quality data from real-world settings from hundreds of sites and operators. The same comparable volume and quality of data—high or standard surgical risk—has not been paralleled in the CEA experience and provides a great deal of unique insight into the evolution of CAS US outcomes, to be discussed further on. These studies, among them CAPTURE (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Unanticipated or Rare Events),¹³ CAPTURE 2,¹⁴ EXACT (Emboshield and Xact),¹⁵ SAPPHIRE WW,¹⁶ and CHOICE (Carotid Stenting for High Surgical-Risk Patients),¹⁷ have studied tens of thousands of patients across hundreds of US operators and sites and have consistently demonstrated that CAS outcomes in the high surgical risk population of patients meets or exceeds the American Heart Association (AHA) guidelines for both symptomatic and asymptomatic patients (Figure 24.1).

In the background (2000–2008), while these pivotal and postmarket trials were being completed and conducted in high-risk surgical patients, the National Institutes of Health/National Heart, Lung, and Blood Institute and Abbott Vascular sponsored the large (2500 subject) CREST (Carotid Revascularization Endarterectomy versus Stenting Trial),¹⁸ which was originally designed to randomize symptomatic patients with standard risk for surgery to either CEA or CAS in 1:1 ratio. As contrasted with the

aforementioned European studies, CREST mandated the use of EPD, included MI as a component of the primary endpoint, and insisted on qualified operators as determined by an interventional oversight committee. The strict qualification criteria for both surgical and endovascular operators used to select sites resulted in over 50% of endovascular applications being rejected¹⁹ and led to a slower than anticipated ramp up of the number of study sites from 2000 to 2004 because there were few US sites with an adequate qualifying volume of CAS activity. Because of new data from the ACST trial published in 2004 demonstrating an advantage of immediate over deferred CEA in patients with asymptomatic carotid lesions, along with an effort to boost the slower than anticipated enrollment, asymptomatic patients were included in 2005, and the study was completed in 2008. The final population was roughly evenly divided between symptomatic and asymptomatic participants.

CREST demonstrated no differences between CEA and CAS for the primary composite endpoint of 30-day death, stroke, and MI, plus ipsilateral stroke to 4 years (7.2% vs 6.8%; *P* = .51) in the intention-to-treat analysis (ITT). In the ITT analysis, periprocedural event rates were the lowest reported for CEA and CAS in a multicenter randomized controlled trial setting. Within these 30-day composite

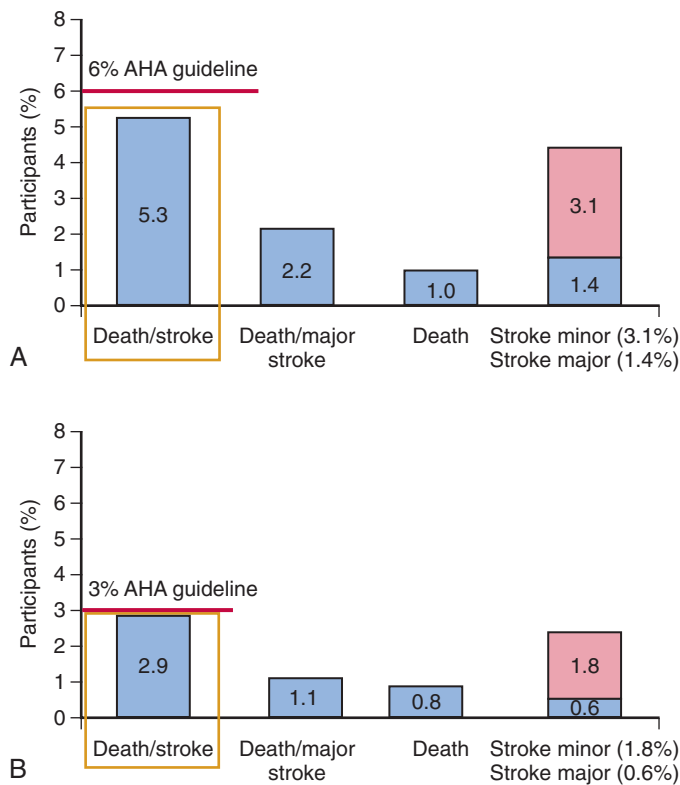


FIGURE 24.1 Combined outcomes from CAPTURE (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Unanticipated or Rare Events) and EXACT (Emboshield and Xact) single-arm studies in high surgical risk patients satisfying American Heart Association (AHA) goals for 30-day outcomes. **A**, In symptomatic patients. **B**, In asymptomatic patients. (Redrawn with permission from Gray WA, Chaturvedi S, Verta P. Investigators and the Executive Committee's thirty-day outcomes for carotid artery stenting in 6320 patients from 2 prospective, multicenter, high surgical-risk registries. *Circ Cardiovasc Interv*. 2009;2:159-166.)

outcomes, there were small differences noted between the therapies: CEA had roughly twice the number of MIs (1.1% vs 2.3%; $P = .03$), and CAS had roughly twice the number of strokes (4.1% vs 2.3%; $P = .01$), the difference being related to the incidence of minor strokes; major strokes were not different between CAS and CEA. Although the trial was not powered to assess these individual components, they served as hypothesis-generating observations and opportunity for outcome improvements. In CREST, the long-term outcomes such as stroke prevention effectiveness, vessel patency, and target lesion revascularization were the same between the two treatment arms, observations that reinforced those also seen in the SPACE and ICSS studies.^{20,21}

The short-term competitive safety profile of CAS was combined with similar comparable long-term durability with CEA represents a unique profile in endovascular intervention. Most, if not all, other endovascular interventions are attractive alternatives to surgery because they can have immediate and similar therapeutic importance to patients without nearly the morbidity associated with the parallel surgical approach (e.g., with abdominal aortic aneurysm repair or lower extremity bypass) but generally suffer from a lack of competitive durability (e.g., SFA stents). In CAS, the long-term durability and stroke prevention being spot on with CEA means that its value and attractiveness really come down to matching the acute

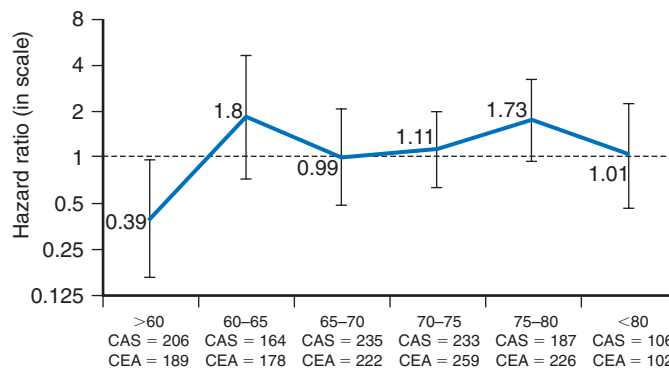


FIGURE 24.2 US Food and Drug Administration analysis of age-related outcomes of carotid artery stenting (CAS) and carotid artery endarterectomy (CEA) from CREST (Carotid Revascularization Endarterectomy versus Stenting Trial) presented with y-axis correctly assigned as logarithmic. (Redrawn with permission from Gray WA, Simonton CA, Verta P. Overview of the 2011 Food and Drug Administration Circulatory System Devices Panel meeting on the ACCULINK and ACCUNET Carotid Artery Stent System. *Circulation*. 2012;125:2256-2264.)

safety profile of periprocedural stroke and death in CEA (which is quite good). If short-term safety outcomes can be matched, then the avoidance of “nuisance” complications such as cranial nerve injury and access site reoperation can become the only real differentiating features between CEA and CAS.

In a separate CREST per protocol analysis (PP) presented to the FDA as part of a successful application for extension of indication (to standard surgical risk patients) of the study devices by the co-sponsor of the study (Acculink stent and AccUNET filter, Abbott Vascular), several other findings were observed.²² First, whereas a best-fit line in the ITT analysis appeared to demonstrate an advantage of CEA over CAS in octogenarians, a direct FDA assessment of this cohort in the PP analysis found that although the adverse outcomes were indeed higher in octogenarians, there were no differences between CEA and CAS in this group (Figure 24.2). Conversely, CAS was found to be safer in the younger than 60-year-old population.

Second, a follow-up assessment of all patients with minor stroke caused by either CEA or CAS demonstrated no differences in the mean severity of neurologic and functional deficit at 1 month and 6 months as measured by National Institutes of Health Stroke Scales (NIHSS) and modified Rankin scale, suggesting that the CAS minor strokes, although more numerous, ultimately had very little lasting clinical impact (Figure 24.3). This confirmed similar findings from previous smaller studies that demonstrated that patients with CAS-related minor stroke were likely to have an NIHSS of 0 or 1 by 1 year.¹² These clinical observations are further bolstered by magnetic resonance imaging data from ICSS that show that although there is a higher frequency of new but asymptomatic diffusion-weighted imaging (DWI) abnormalities after CAS compared with CEA, in fact, the volume of abnormalities is similar.²³ Not only are there fewer but larger CEA-associated defects than CAS in ICSS, but the CEA lesions were also more likely to convert from acute to persisting lesions (relative risk, 0.4; 95% CI, 0.2–0.8; $P = .007$).²⁴ The clinical implication of these findings is unclear but seems to support the data on the increase in minor stroke events

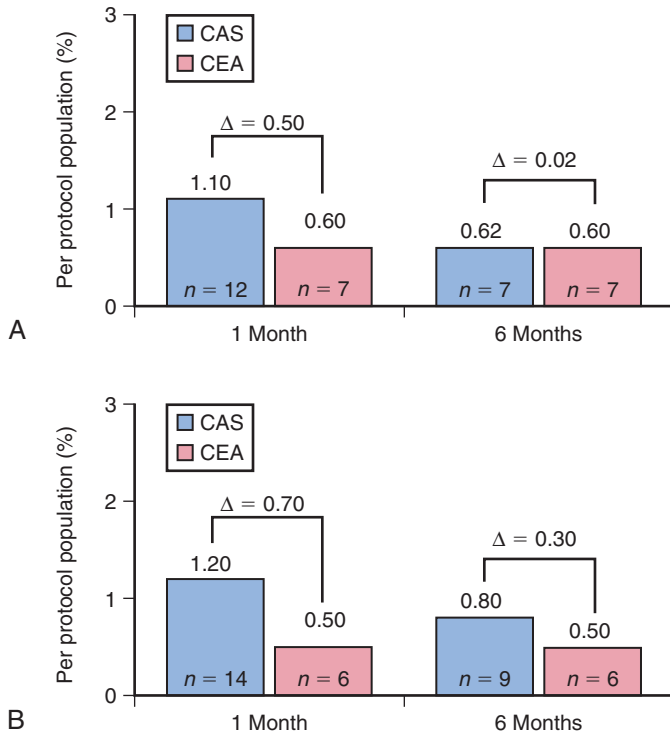


FIGURE 24.3 Outcomes of participants experiencing a minor stroke related to either carotid artery stenting (CAS) or carotid artery endarterectomy (CEA). **A**, National Institutes of Health Stroke Scale. **B**, Modified Rankin Scale. (Redrawn with permission from Gray WA, Simonton CA, Verta P. Overview of the 2011 Food and Drug Administration Circulatory System Devices Panel meeting on the ACCULINK and ACCUNET Carotid Artery Stent System. *Circulation*. 2012;125:2256-2264.)

seen in CREST with CAS compared with CEA but the relative lack of persistent symptoms.

The CREST PP analysis also found that there appeared to be an important trend of outcome improvement within the CAS operators over the 8 years of the study enrollment (Figure 24.4) but that there was no similar trend within the CEA operators. These observations were not surprising given the 60-year experience with CEA and stable techniques and established patient selection criteria at the start of the study, but for CAS, the lack of even FDA-approved and dedicated devices and very limited broader experience until the fourth year of the study.

This last finding in CREST, the improvements in CAS outcomes within the trial, cannot entirely be explained by the experience accrued within the trial because the average number of CAS cases performed by interventionalists was around six. This is where an intersection of the unique reimbursement hurdles delaying a fuller adoption of CAS as an alternative to CEA or medical therapy requires comment for a fuller understanding of the therapy and its outcomes and status. Specifically, carotid intervention has been under a restrictive national coverage decision (NCD) since the 1980s as a result of a negative technology assessment of carotid angioplasty alone and that did not foresee the advent of stenting at the time. This NCD, which did not support coverage or payments for carotid, vertebral, or intracranial intervention, was modified in the early 2000s to allow for research in CAS and then again in 2005 after FDA approval of the first CAS systems. This second NCD

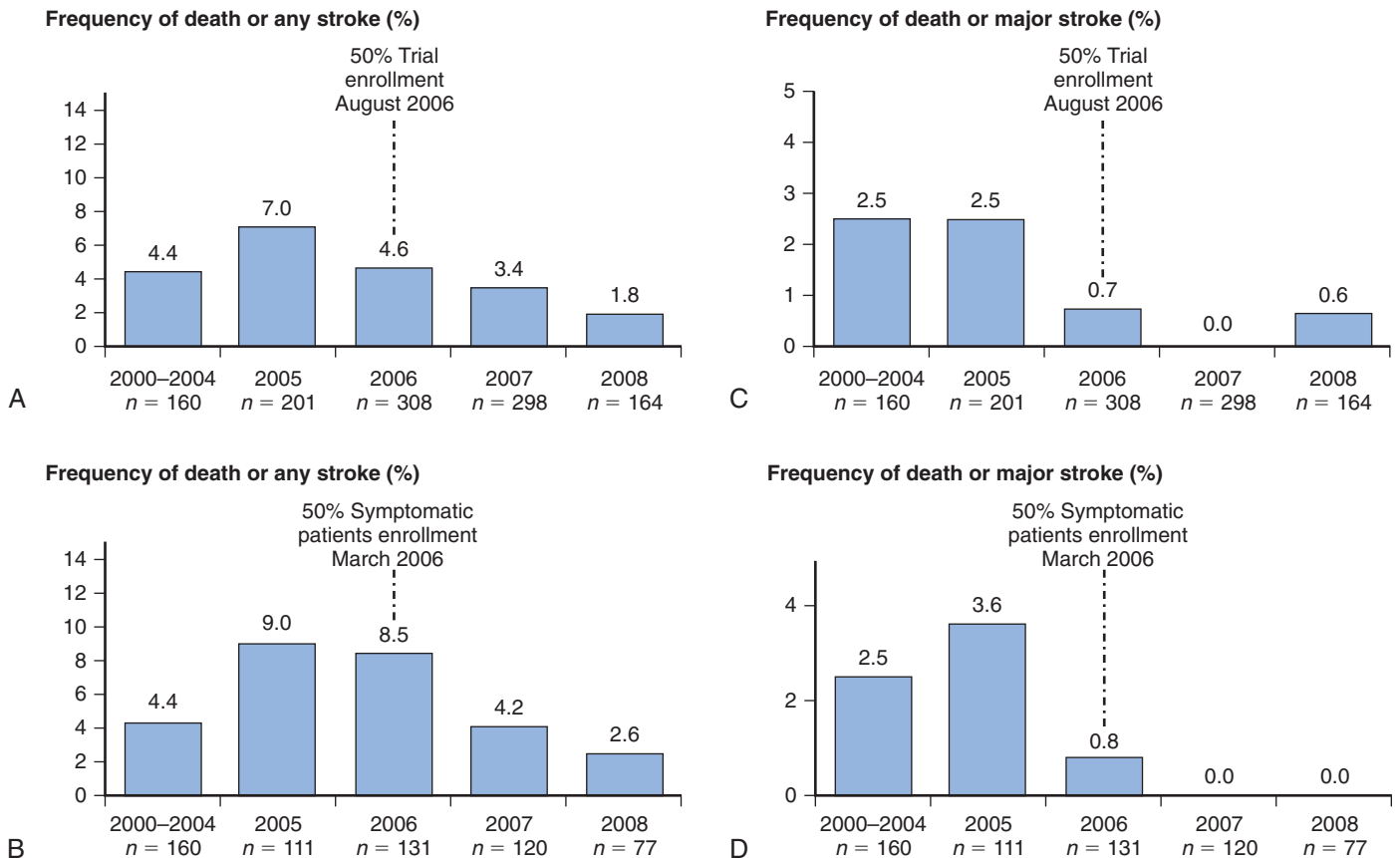


FIGURE 24.4 Outcome improvement demonstrated within the later phases of CREST (Carotid Revascularization Endarterectomy versus Stenting Trial) in the carotid artery stenting (CAS) arm. (Redrawn with permission from Gray WA, Simonton CA, Verta P. Overview of the 2011 Food and Drug Administration Circulatory System Devices Panel meeting on the ACCULINK and ACCUNET Carotid Artery Stent System. *Circulation*. 2012;125:2256-2264.)

modification extended coverage to patients with high surgical risk with recent symptoms, which represents a small (estimated to be 10%–15%) fraction of the overall population of patients requiring carotid intervention. The 2005 NCD also allowed for coverage of CAS postmarket registries mandated as a condition of FDA approval that were subsequently extended by the sponsors voluntarily to explore other scientific queries and that ultimately allowed greater patient access to and operator activity in CAS. During the time of this coverage of registry activity, a great deal was learned and published about the technique and patient selection related to CAS that have been reflected in this chapter and have accrued to the benefit of patients not just in the United States. A recent analysis of the past decade of CAS outcomes strongly backs the concept that CAS outcome improvement seen in CREST was the result of FDA approval (2004) and Centers for Medicare & Medicaid Services (CMS) reimbursement (2005), which supported a much broader and deeper parallel CAS experience outside of CREST, gained primarily in the postmarket studies.²² These studies allowed the treatment and study of more than 50,000 patients in the last half of the decade, which generated high-quality prospective 30-day data across hundreds of sites and unparalleled in any CEA experience. This volume of activity dwarfs the first half of the decade when a few small (generally <400 patients) trials in only a few sites (<30) and a few operators provided the only experience for CAS using EPDs in this country. This marked increase in the number of CAS cases being done in the second half of the decade resulted in dramatic improvements in not only the IDE trial results across stent systems but also within the same stent and EPD systems (Figure 24.5).

Following CREST, ACT-I (Asymptomatic Carotid Trial) was another large (1453 participants) US-based study (Abbott Vascular) randomizing between CAS and CEA in good surgical risk patients specifically to compare outcomes in asymptomatic patients for noninferiority.²⁵ CAS was found noninferior to CEA both for the secondary endpoint of stroke and death at 30 days (2.9% and 1.7%, respectively) and for the primary endpoint (which added ipsilateral stroke after 30 days) at 5 years (3.8% and 3.4%, respectively), with a highly protective effect of revascularization in either arm (<1%/year ipsilateral stroke risk).

An even larger UK government-sponsored global (33 countries, 130 centers) effort recruited 3625 participants with asymptomatic carotid stenosis and evenly randomized them between CAS and CEA, with the use of stent device and EPD left to the operators.²⁶ There were no differences in the two groups for disabling stroke at 30 days (~1%) or for the primary endpoint of 5-year K-M estimate for all stroke or fatal or disabling stroke.

Taken together, the ACST-2 and ACT I trials demonstrate remarkably consistent results with very low rates of major adverse procedural events and low rates of stroke after successful revascularization with either therapy in asymptomatic patients with severe carotid bifurcation stenosis.

In retrospect, much of the failure of the earlier European trials to have adequate experience in their operators can be explained by the era when they were both planned and executed; had the studies been done in the

second half of the decade rather than the first, the results may have been appreciably different for analogous reasons. Similarly, had the CREST trial enrollment not lagged—the last 4 years of the trial (2005 to 2008) enrolled the significant majority of participants—as a result of the lack of adequate operator experience because of the enforcement of stringent operator selection criteria, then outcomes may have more closely paralleled the EU's.

Unfortunately, there has been a recent marked reduction of CAS activity in the United States as a result of a unique and persistent refusal by the CMS to expand coverage to devices approved or cleared by the FDA as safe and effective despite a number of national coverage determination processes and opportunities to do so. Given the data on outcome improvement in the United States with volume activity that have just been discussed, this has real implications not only for patient access to care but also the quality of their outcomes. It also may make recruitment of qualified sites for CAS research problematic as well as put a damper on spending for technology improvements that can further safeguard patient outcomes.

As has been detailed, the clinical event rates for CAS and CEA are quite low, a happy fact for patients and referring and treating physicians alike; however, this is an unfortunate fact for researchers seeking to compare outcomes across therapies or to improve outcomes within therapies because it means that very large trials are required to assess differences. As an example, an intervention that seeks to demonstrate a 1% difference in outcomes in stroke would mean a study of several thousand patients, and recruitment for trials of this size—even with brisk enrollment—can take close to a decade, by which time the technology or method can be obsolete. So, in addition to the “classic” clinical outcome measures listed, attempts to define objective but nonclinical differences in techniques and equipment have used surrogate, mechanistic markers of safety. These have primarily centered around the detection—the microembolic signals detected on transcranial Doppler—or consequence—new lesions seen on serial magnetic resonance diffusion-weighted imaging (MR-DWI)—of microemboli. The former method is confounded by the lack of reliable ability to distinguish gaseous from solid emboli, which means that presumably innocuous microbubbles released from moving devices through sheaths, unsheathing filters and stents, and even contrast injection are counted among potentially harmful ones; even still, it can be useful in characterizing potentially vulnerable stages of the procedure even if its use is encumbered for comparative purposes.²⁴ In the case of the latter technique, it is preferred because these overwhelmingly clinically silent imaging findings—the result of the cellular edema indicative of cellular ischemia—are counted with consistency and are frequent enough to be used to distinguish both between therapies (i.e., CAS and CEA) and within (e.g., differences among EPD systems) requiring a relatively small number of patients.²⁷ Although the appearance of incidental or background MR-DWI findings in noninterventional patients have been associated with increased incidence of dementia, it should nevertheless be emphasized that although these markers will likely have utility in determining such things

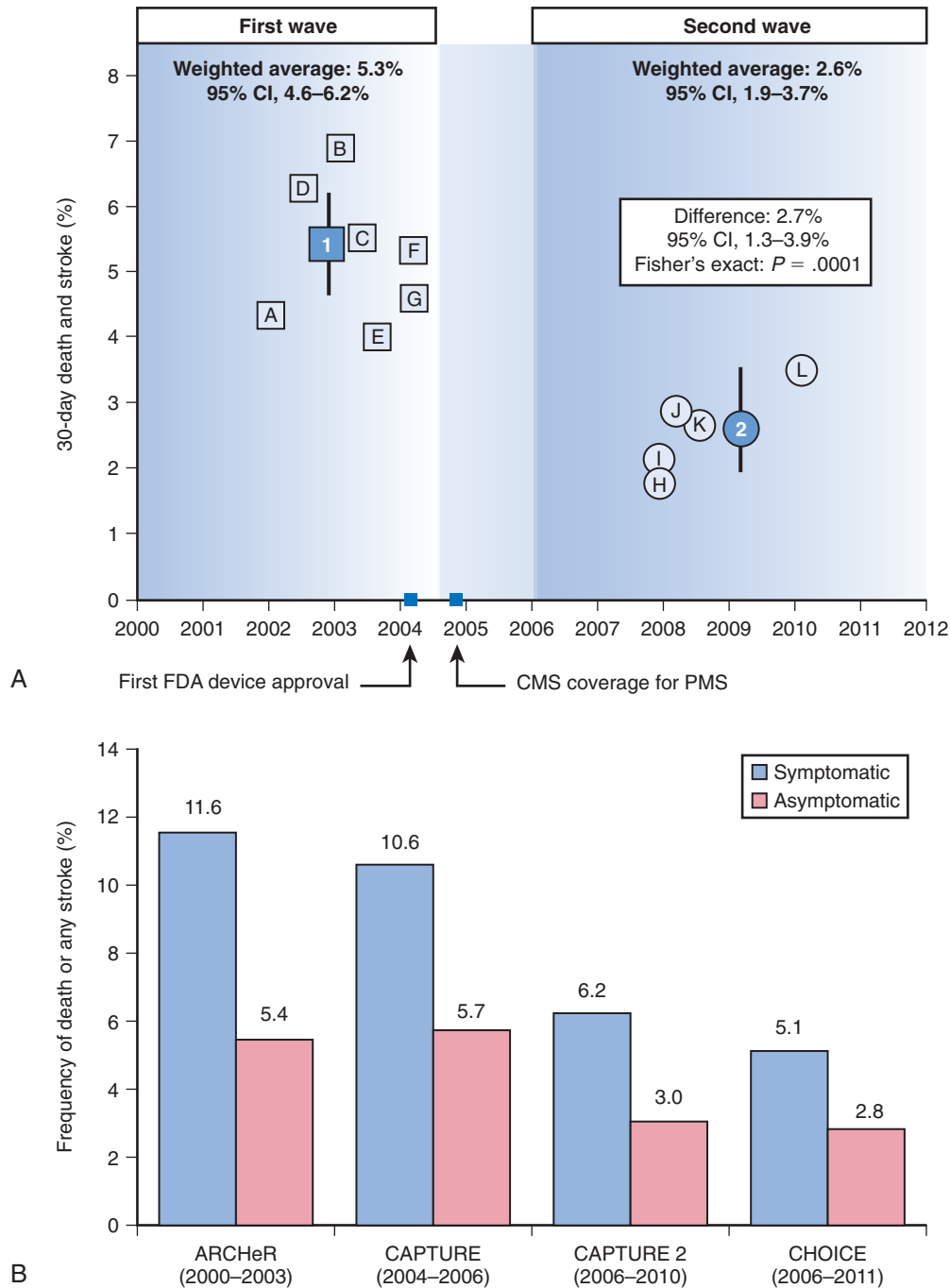


FIGURE 24.5 **A**, Improvement in outcomes among US Investigational Device Exemption IDE trials testing different carotid artery stenting (CAS) systems demonstrates a halving of complication rates with the approval of device and commensurate increase in clinical procedural volumes. **B**, Similar outcome improvements over the same time period using a single CAS system. *ARChR*, ACCULINK for Revascularization of Carotids in High-Risk patients; *CAPTURE*, Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Unanticipated or Rare Events; *CHOICE*, Carotid Stenting For High Surgical-Risk Patients; *CMS*, Centers for Medicare & Medicaid Services; *FDA*, Food and Drug Administration; *PMS*, post-market approval study. (Redrawn with permission from Gray WA, Simonton CA, Verta P. Overview of the 2011 Food and Drug Administration Circulatory System Devices Panel meeting on the ACCULINK and ACCUNET Carotid Artery Stent System. *Circulation*. 2012;125:2256-2264.)

as the effectiveness of EPDs or the effects various access approaches or tools have on these measures of microembolism, there has yet to be a clinical correlate directly linked to these strictly image-based findings. That said, the low but real rate of minor stroke excess seen in CAS compared with CEA, especially in symptomatic patients, appears to roughly parallel in a proportional way the consistent excess in MR-DWI lesions noted postprocedure. Therefore, both in-

tuitively and on a semi-empiric basis, the reduction of MR-DWI lesions is desirable.

Last, although several publications have reported the effects of CAS (and CEA) on subtle measures of cognition using the outcomes of neuropsychometric testing,^{28,29} the results have been mixed and far from conclusive, likely related to the difficulty in administering these tests reliably and multiple confounders, known and unknown.

The Procedure

The endovascular management of obstructive atherosclerotic bifurcation carotid disease is practiced by multiple specialties—interventional cardiology, vascular surgery, neurointerventional radiology, and interventional neurology—and so mandates a confluence of disparate skill sets and understanding of both the disease process as well as the exceptionality of the procedure. This section discusses the relevant elements of endovascular carotid intervention important to performing it expertly and safely.

The predicate of surgical plaque removal (CEA) of atherosclerotic bifurcation carotid disease has been performed for more than 60 years³⁰ and has been demonstrated to reduce future stroke in both symptomatic and asymptomatic patients as compared with deferred therapy.^{3,31-33} Although acknowledging that these trials lacked a programmed, monitored, and modern medical therapy component, they nevertheless represent the highest quality data available (prospective, randomized, controlled, multicenter) to both direct clinical decision making and, in the case of CAS, use as a comparator for the standard of care. As was seen in the first half of this carotid section, the progression of carotid testing and therapy has always been predicated on a comparison, direct or indirect, with CEA.

The carotid artery and associated atherosclerotic plaque are unique not only as pathophysiologic determinants of clinical ischemic syndrome but also in their response to intervention, surgical or endovascular. On the first point, it is only in the small minority of cases that symptoms related to carotid stenosis are due to an actual reduction in distal blood flow, as contrasted with all other atherosclerotic stenoses, which create their associated clinical syndromes via restriction in distal bed perfusion—chronic or acute. As a further demonstration of its distinctive nature, an acute occlusion of the carotid artery can often be asymptomatic. All of these characteristic aspects are related to the maintenance of distal perfusion by the circle of Willis, which although complete in less than half the population, nevertheless provides perfusion adequate enough to avoid symptoms in many cases.³⁴ Regarding the second point, the carotid bifurcation plaque, in the significant majority of lesions, is reliably and discretely localized within about 2 cm of the bifurcation. This fact is a result of the flow dynamics within the carotid bulb that set up a flow eddy responsible for lesion generation,³⁵ and this allows for its easy and routine surgical removal—not true in many other atherosclerotic vascular territories. In addition, the durability of carotid intervention is unmatched in the arterial circulation: long-term rates of restenosis requiring re-intervention for both CEA and CAS are similar and low—1% to 2% per year.¹⁸ In the case of standard (not eversion) CEA, enlargement of the arteriotomy with a patch is associated with lower rates of restenosis, especially in women,³⁶ whereas in CAS, no definitive association with residual stenosis or sex and long-term patency has been shown. Understanding these two unique qualities of the carotid bifurcation drives decision making in the procedural components of CAS.

Although an in-depth exploration of the subject is largely beyond the scope of an interventional chapter on CAS, it is important to at least acknowledge the indications

for carotid intervention in general terms, and for CAS specifically, and that some of them are in evolution or testing. These were codified in a 2011 multi-society guidelines document that the following distillation references³⁷ (Table 24.3).

In clinical practice, symptomatic patients with stenoses greater than 70% are offered CEA or CAS without delay because it appears that any salutary effect of intervention is greatest in the first 2 to 4 weeks, although women have a particularly rapid drop-off in the benefit after the first 2 weeks.³⁸ For symptomatic patients with stenosis between 50% to 70%, which is a small fraction of the affected population, the benefit is less, and these cases should be taken on a case-by-case basis, and a determined search for other potential causes of a cerebrovascular event should be considered (i.e., occult atrial fibrillation).³⁹ In asymptomatic patients, most operators do not offer an intervention unless the lesion is at least greater than 70% to 80% in combination with a life expectancy of at least 5 years. This is because the natural history of an “unmolested” severe asymptomatic carotid plaque has neurologic event rates of roughly 2% to 3% per year,³² and the risk of CEA or CAS must be amortized over a sufficient time period to provide a clinically meaningful improvement for the patient. The most recent data available for the 30-day risk for both CEA and CAS suggest that the stroke and death rate is between 1.5% and 2.0%,^{18,40} nearly half what it was in some of the landmark, now legacy, CEA studies (ACAS and ACST) in which the non-CEA arm of medical therapy was not strictly controlled. Accordingly, a great deal of speculation has arisen that improved modern medical therapy may have lowered the above rates of stroke in asymptomatic patients in observational settings such that intervention may no longer be justified^{41,42}; however, the only randomized data that exist support CEA and, by extension, CAS. The CREST 2 trial is intended to examine this question by randomizing asymptomatic patients with severe bifurcation carotid stenosis to either optimized and intensive medical therapy or intervention with CEA or CAS (which will be combined as the “treatment arm” for purposes of statistical comparison); this trial is only a few hundred patients away from its target enrollment at the time of this writing, so outcomes will not be known for several more years. Finally, it is important to acknowledge that CAS has not yet been tested directly versus medical therapy in either the symptomatic or asymptomatic populations; any proposed benefit of CAS is extrapolated primarily from its trial comparisons with CEA.

The performance of the CAS procedure has some variability depending on the type of embolic protection that is used, but otherwise, it can be divided into the following steps: establish access, place EPD, balloon dilation (pre- and poststent), stent placement, and retrieval of embolic protection. Each step has to be considered within the anatomic and clinical environment at hand, the latter of which can be quite dynamic at times. Although it takes less than 7 to 10 minutes of EPD dwell time to perform a CAS well, compared with most other endovascular procedures (except for some neurointerventions), performing a successful CAS requires careful planning and unbroken attention during that short but intense time because of the

TABLE 24.3 Summary of Multidisciplinary Guidelines on the Management of Carotid Disease

INDICATION	RECOMMENDATION (CLASS)	LEVEL OF EVIDENCE
Symptomatic High Surgical Risk		
Among patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk of surgery, or when other specific circumstances exist, such as radiation-induced stenosis or restenosis after CEA, CAS may be considered when performed by an experienced operator.	IIa	B
It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery.	IIa	B
Symptomatic Average Surgical Risk		
CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the ICA is reduced by >70% as documented by noninvasive imaging or >50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is <6%.	I	B
CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the ICA is reduced by >70% by noninvasive imaging or >50% by catheter angiography.	I	B
Asymptomatic High Surgical Risk Patients		
Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, such as expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences.	I	C
It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery.	IIa	B
Asymptomatic Average Surgical Risk Patients		
Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasonography), but its effectiveness compared with medical therapy alone in this situation is not well established.	IIb	B

CAS, Carotid artery stenting; CEA, artery endarterectomy; ICA, internal carotid artery.
From White CJ. Carotid artery stenting. *J Am Coll Cardiol*. 2014;64:722-731.

potentially catastrophic neurologic outcomes from even a small error or lapse in method or judgment. In addition to these technical considerations, the stent pharmacology (control of anticoagulation, pre- and postprocedure medications), vascular access, hemodynamic and neurologic shifts, and so on must all be accurately identified and successfully managed, typically mandating a broad and deep preparedness to do so by not just the operator but the larger care team as well.

In uncomplicated CAS, some practitioners feel comfortable discharging patients on the same day given the very low rates of overall complications. This appears to be a reasonable, though aggressive, strategy of patient management; however, it can potentially miss late stroke identification, which although numerically very small, requires an independent evaluation up to 24 hours after the procedure.

Lesion Considerations

Lesion assessment is a very important component of procedural planning, and proper lesion selection can lead to improved patient outcomes. To start with, using the appropriate method to determine the angiographic lesion severity and thus the indication for CAS in the first place is critical. Although there are several methods (e.g., European Carotid Surgery Trial [ECST] method),⁴³ the one on which landmark trial data are based and therefore accepted in the United States is the NASCET criteria.⁴⁴ In this

method, the angiographic lesion minimum lesion diameter (MLD) in the worst angiographic projection is used as the numerator and the distal internal carotid artery (ICA) where the vessel stops tapering as the reference segment in the denominator (Figure 24.6). If the NASCET criteria are strictly adhered to and the typical human distal ICA reference diameter is 5.0 to 5.5 cm, then in an asymptomatic patient, the lesion MLD will be about 1 to 1.5 mm (which equals a 70%–80% lesion). It is useful to bear this rule of thumb in mind because it is easy for the eye to be drawn to the larger common carotid artery (CCA) or carotid bulb diameter and overestimate the true stenosis.

Beyond the stenosis severity, there are lesion qualities that must be assessed before considering or performing CAS, including filling defects consistent with thrombus, degree and pattern of calcification, length of lesion, and associated tortuosity or angulation. Although some operators report successful CAS in the presence of thrombus (and have advocated proximal protection in these situations) and lesions producing recent cerebrovascular symptoms almost certainly have some degree of thrombus even if not identifiable angiographically, generally speaking, visible thrombus has been a contraindication for CAS in patients with reasonable surgical alternatives. Heavy calcification, especially in a circumferential pattern, is associated with stent underexpansion and stent delivery system entrapment along with the potential for more pronounced hemodynamic instability and is considered a rel-

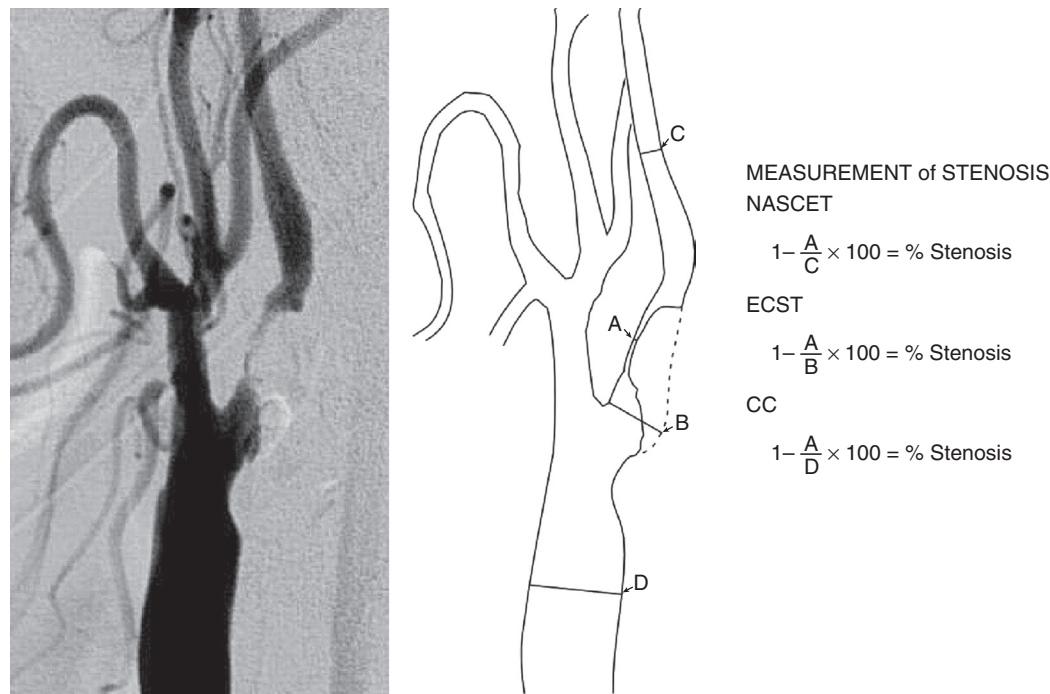


FIGURE 24.6 The NASCET (North American Symptomatic Carotid Endarterectomy Trial) method of carotid stenosis determination. *ECST*, European carotid surgery trial. (From Higashida RT, Meyers PM, Phatouros CC, et al. Technology Assessment Committees of the American Society of Interventional and Therapeutic Neuroradiology and the Society of Interventional Radiology. Reporting standards for carotid artery angioplasty and stent placement. *J Vasc Interv Radiol.* 2004;15:421-422.)

TABLE 24.4 Carotid Artery Stent Patient and Procedural Factors Likely to Be Associated with Adverse Procedural Outcomes

MEDICAL COMORBIDITY	ANATOMIC CRITERIA	PROCEDURAL FACTOR
Older adult (older than 75 or 80 y)	Type III aortic arch	Inexperienced operator or center
Symptom status	Vessel tortuosity	EPD not used
Bleeding risk or hypercoagulable state	Heavy calcification	Lack of femoral access
Severe aortic stenosis	Lesion-related thrombus	Time delay to perform procedure from onset of symptoms
Chronic kidney disease	Echolucent plaque	
Decreased cerebral reserve	Aortic arch atheroma	

EPD, Emboli protection device.
From White CJ. Carotid artery stenting. *J Am Coll Cardiol.* 2014;64:722-731.

ative contraindication to CAS. Poorer outcomes have been associated with diffuse, long lesions and those requiring multiple stents⁴⁵ and should be approached with caution. Last, angulation that is suboptimally located at or just distal to the bifurcation can lead to difficulty with wire, filter, or stent transit and can make filter retrieval difficult (Table 24.4). Experienced operators will elect to reconsider CAS in favor of CEA or medical therapy when faced with one or multiple of these attributes and in that way will deliver the best outcomes for the patient, with the understanding that *these therapies are complementary, not competitive*.

Access

Access to the CCA via the common femoral artery is typically achieved using a 6-Fr straight sheath (with exceptions noted later), although outside of the United States, guide catheters with preformed shapes are also available for use. Some stent devices have smaller delivery system calibers that may allow for 5-Fr sheath use, and although these may be attractive from both radial and femoral

access perspectives, the trade-off can be a significant loss of guide stability and support. If proximal protection is to be used, it is done with a specialized 9-Fr catheter that has an occlusion balloon on its tip and the capacity to place a second occlusion balloon into the external carotid artery (ECA). Some operators practice radial artery access for CAS as an alternative to femoral access to avoid or minimize both access site complications but also aortic arch interaction.⁴⁶ Last, it has been demonstrated that up to about 35% of strokes associated with CAS may be related to an aortic arch source liberated while establishing access,⁴⁷ so direct carotid access for carotid stent placement has been proposed as an alternative to transfemoral CAS. A commercial system (Silk Road Medical) that uses a high-flow reversal system not requiring external carotid occlusion to establish the proximal protection has been developed on the plausible logic—and early data—that arch avoidance leads to fewer MR-DWI lesions—a marker of cellular edema resulting from cell death—and ultimately fewer strokes.⁴⁸ This system requires a small surgical incision in the proximal CCA to establish access, a CCA largely

free of atherosclerotic involvement, and at least 5 cm of distance from the supraclavicular arterial access point to the carotid bifurcation. Of note, although the MR-DWI and clinical data have been very good for this transcatheter artery revascularization (TCAR) approach,^{49,50} garnering FDA clearance and CMS reimbursement coverage across the broad spectrum of patients with bifurcation carotid stenosis, there are no multicenter randomized data to help with comparative assessments to CEA or transfemoral CAS. Nevertheless, it has been broadly adopted by the carotid surgical community as the preferred carotid revascularization method in many practices.

Arch anatomy, proximal CCA tortuosity, or disease and lesion location individually or in combination determine both the difficulty of CCA cannulation and sheath placement as well as the method used to gain access. In straightforward anatomy, a support wire is ultimately positioned into the ECA by way of a diagnostic catheter that is advanced into the ECA over a softer wire first. The interventional sheath is then substituted for the diagnostic catheter, and the interventional procedure can begin. If the carotid bifurcation is involved with significant occlusive disease, making wire passage into the ECA dangerous or anatomically prohibitive, an alternative method involves placing a support wire shaped with a tight pigtail-style curve or using newer wires with a hydrophilic tip and a moderate support body in the CCA just below the bifurcation and advancing the sheath over those arrangements. As long as there is enough CCA length and minimal angulation or tortuosity, these methods can be safe and effective in establishing access, but in shorter CCAs, it may not be possible to have enough wire support in place to allow sheath placement.

If there is significant CCA tortuosity, then access can be challenging in a number of different ways. First, negotiating a wire, followed by even a diagnostic catheter

into the CCA, can be problematic. Second, even if a sheath can be successfully placed, it can result in associated changes in the more distal vessel by displacing the proximal tortuosity more distally in a vessel that is ultimately fixed between two points in its proximal origin (aorta) and distal terminus (petrous carotid), which can make later procedural steps (filter or stent placement) difficult, risky, or impossible. Last, and especially when working in the right CCA, if a reasonably coaxial position of the sheath in the CCA cannot be established because of tortuosity, then dissection of the CCA caused by catheter tip trauma becomes a distinct possibility as well.

If the aortic arch is heavily involved with atherosclerosis, then even the most expert catheter manipulation can lead to embolic complications. There are also anatomic arch variants, the most common (~25%) and relevant of which is a bovine origin of the left CCA (i.e., originating from the innominate trunk), which can often be further retroflexed and lead to difficulty in cannulation or a stable coaxial position (Figure 24.7). In addition, the aorta can elongate and rotate with age and in the case of the aortic arch, pinned between the sternum and the spine, an exaggerated “hump” or apex is established along with the proximal displacement of the great vessels. These changes are categorized into three types:

- Type I arch is normal with the great vessels arising from a normally shaped apex.
- Type II arch has a proximal displacement of the great vessels with a moderately peaked arch.
- Type III arch has an accentuated peak and marked proximal displacement of the great vessels.

The great vessels functionally appear to arise from the ascending aorta in the more complicated arches (Figure 24.8). These arch challenges require more aggressive, reverse-shaped catheters such as the Simmons catheter (Cook) and

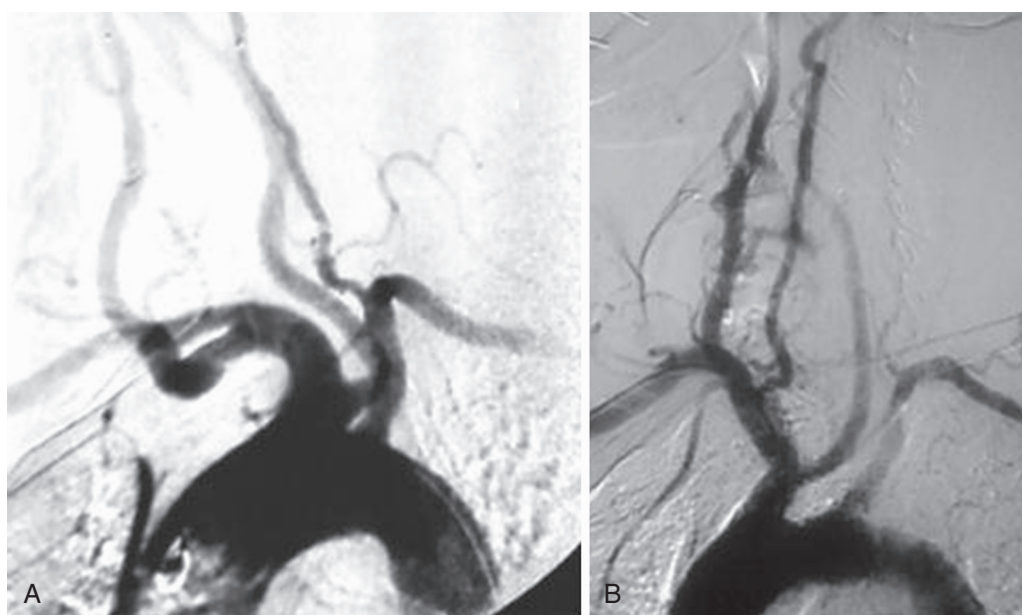


FIGURE 24.7 Examples of bovine arch variation anatomy demonstrating the origin of the left common carotid artery (CCA) from the innominate trunk. In addition, in A, there is additional tortuosity in both the right and left CCA. (From Liapis CD, Efthimios D, Avgerinos D, Chatziioannou A. The aortic arch: markers, imaging, and procedure planning for carotid intervention. *Cath Lab Digest*. 2009;17:6.)

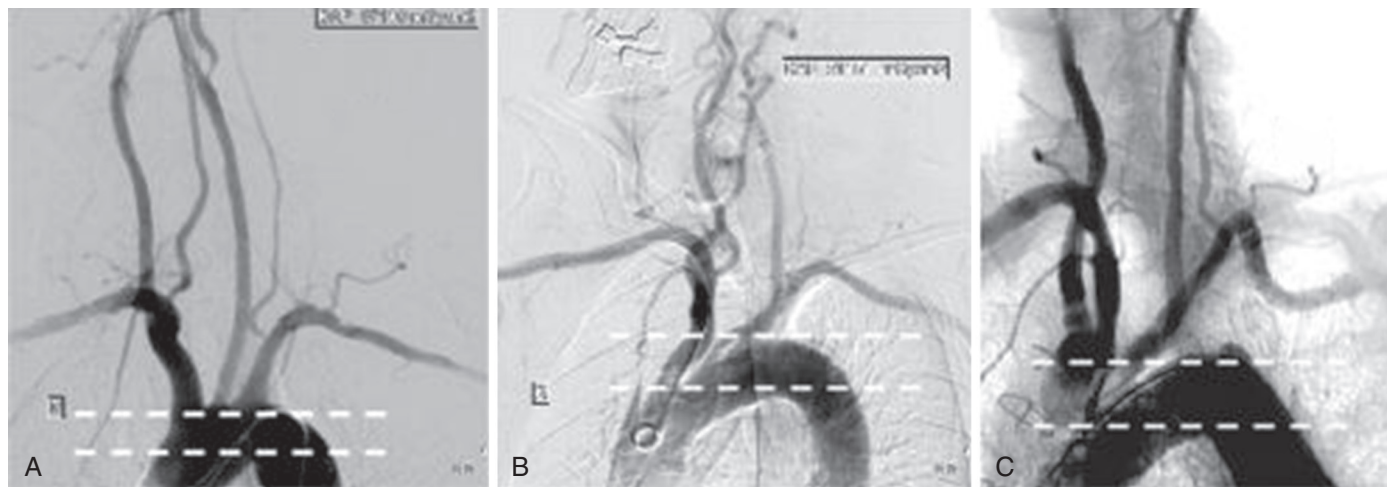


FIGURE 24.8 **A**, Type I aortic arch with great vessels arising from the apex. **B**, Type II aortic arch with moderate proximal displacement of the great vessels. **C**, Type III aortic arch with severe proximal displacement of the great vessels. (From Liapis CD, Efthimios D, Avgerinos D, Chatziioannou A. The aortic arch: markers, imaging, and procedure planning for carotid intervention. *Cath Lab Digest*. 2009;17:6.)

TABLE 24.5 Markers of Aortic Arch Anatomic Features Determining Difficulty with Carotid Access

	FAVORABLE	UNFAVORABLE
Arch elongation	Types I and II	Type III
Arch vessel	Separate origins of three configurations	Bovine variation arch branches (left carotid access)
Arch calcification	No or a trace of	Luminal irregularity or calcium shadowing diffuse calcification
Arch vessel origin stenosis (%)	<50	>50

From Liapis CD, Efthimios D, Avgerinos D, Chatziioannou A. The aortic arch: markers, imaging, and procedure planning for carotid intervention. *Cath Lab Digest*. 2009;17:6.

typically multiple attempts with multiple tools until the correct combination of catheters are found, all of which can lead to greater risk of embolic complication (Table 24.5). In fact, some speculate that adverse outcomes in octogenarians are likely caused by the difficulty in overcoming the greater incidence of age-related aortic distortion. Therefore, it has become standard practice to obtain cross-sectional imaging (computed tomography angiography or magnetic resonance angiography) as part of the preprocedural planning to better assess risk and appropriateness of the CAS option.

When the listed access challenges occur in isolation but not in the extreme, they have a reasonable chance of being safely overcome by an experienced and skilled operator. However, when they occur in the extreme or in combination, establishing safe access via femoral or radial access can be impossible or highly risky and should be abandoned in favor of medical therapy, direct carotid access CAS, or CEA, assuming the patient is eligible. Always in the operator's mind should be the preprocedural estimation of stroke risk to the patient, which is no longer accurate after the specific anatomic access difficulties are encountered. This change in procedural risk should cause a reconsideration of the recommendation of CAS in the first place. A determined and unsuccessful, but uncomplicated, attempt at access should not be considered in any way a failure; quite the opposite—it demonstrates good clinical and procedural judgment.

Embolic Protection

After access is achieved, embolic protection needs to be established. EPD comes in two basic varieties depending on their placement relative to the lesion: (1) distal, with the intent of either blocking (occlusion balloons, which are not used with any frequency any more but were in fact the first available form of EPD) or capturing (filters) any debris that might be liberated during the course of the CAS procedure, or (2) proximal, with the intent of stagnating or reversing carotid flow so that no liberated debris can even achieve cranial travel. There are various styles of filter construction, the qualities of which can be divided into their type of support frame, such as full, partial, and hoop; their means of actuation (because all filters are placed through the lesion in a constrained low-profile) such as outer sheath withdrawal or remote proximal handle deployment, fixed wire versus bare wire; and more detailed features such as the number, size, and pattern of pores (which determine flow dynamics), filter membrane materials, tip crossing profiles, and so on (Figure 24.9). In difficult anatomy, the bare wire systems Emboshield NAV 6 (Abbott Vascular) and Spider Rx (Medtronic) have the advantage of being able to negotiate tortuous anatomy with a free wire first without having the burden of the filter frame to stiffen the system and lessen the performance of the wire. Because clinical event rates in CAS are low, a randomized head-to-head comparison on outcomes

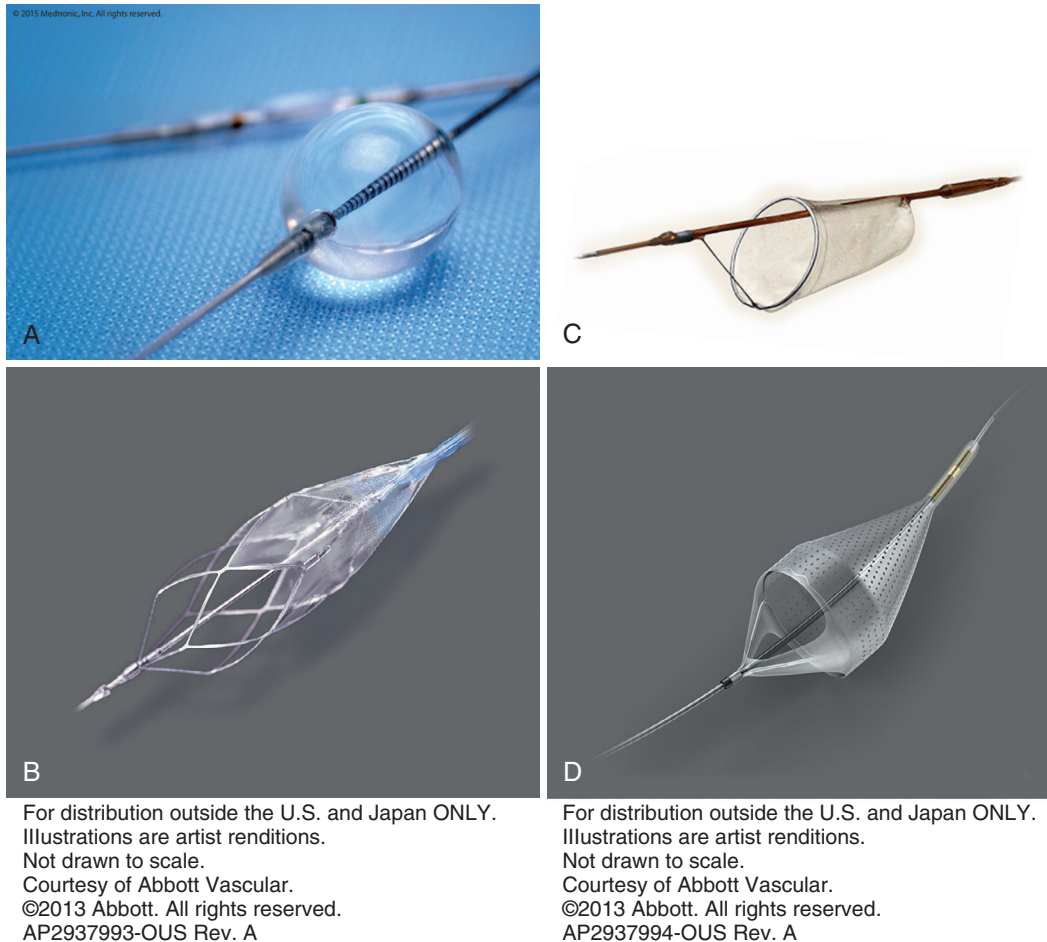


FIGURE 24.9 Various forms of distal embolic protection devices. **A**, GuardWire (Medtronic). **B**, AccUNET. **C**, FilterWire EZ (Boston Scientific). **D**, Emboshield. (**B** and **D**, Courtesy of Abbott Vascular. © 2013 Abbott. All rights reserved. **C**, From Dr. Jonathan D. Marmur, www.marmur.com/carotid-artery-stenting.html.)

between filters would require several thousand patients to demonstrate a difference and has yet—and will likely never be—performed. Furthermore, any retrospective analyses of filter outcomes are generally not only underpowered but also suffer from potential selection bias.⁵¹

The most representative comparative data on filters available come from retrospective analyses of high-quality, large, all-comer prospective registries in high surgical risk patients when operators did generally not have a choice of EPD. Although stents were also different between studies (more on that later but suffice to say that there is no definitive measurable effect regarding differential stent outcomes either), there was no difference in outcomes between filters in demographically similar and contemporaneously treated cohorts of several thousand patients.¹⁵ Therefore, the choice of filter type is typically based on operator familiarity or comfort, anatomic considerations, and experience with one or multiple devices. If the operator volume is relatively low, most operators select a workhorse EPD and use it almost exclusively (Video 24.1).

A newer embolic protection strategy called the Neuroguard System (Contego Medical) involves the concept of double filter protection; that is, a standard wire-based distal embolic filter is combined with a filter mounted to the tip of a combined balloon and stent delivery catheter

that is remotely actuated by a handle mechanism. Typical distal filter pore size diameter is at least 100 μm to allow for adequate flow and minimal thrombus formation during the CAS procedure dwell time. Because the Neuroguard filter is only deployed during stent deployment and post-stent balloon inflation for only a couple of minutes, the pore size can be significantly reduced to 40 μm . In a small trial, this has resulted in very good clinical outcomes, 100% particulate capture in the filter of which 90% were less than 100 μm in size, and a reduction in new ipsilateral lesions on MR-DWI to near gold-standard CEA levels.⁵² Based on these promising results, there is now a pivotal IDE trial in the United States that is currently enrolling.

Proximal protection comes in two main varieties: percutaneous flow cessation (Mo.Ma device, Medtronic) and flow reversal (Neuro Protection System, WL Gore, and the surgical TCAR System, Silk Road Medical) (see Figure 24.9). Both percutaneous devices seek to recapitulate the surgical management of flow during CEA and hence similar embolic protection by occluding both the ECA and CCA using soft, volume-based, elastomeric balloons placed in each location. This prevents antegrade flow (CCA balloon) and retrograde flow (ECA balloon), both of which result in no flow into the distal circulation. The Gore device creates an arteriovenous shunt to maintain a continuous reversal of flow

into the venous circulation (via femoral vein) through a large filter. The Medtronic device maintains flow cessation, and the static column of blood that results and any material released during the procedure is then cleared through multiple aspirations at the end of the procedure until the sieved material is clear of debris. Both transfemoral devices appear to result in slightly lower rates of stroke in both their pivotal trials as well as in a meta-analysis,⁵³⁻⁵⁵ although a similar low rate of complication was seen with a second-generation distal filter device.⁵⁶ Supporting the possibility of differential protection, however, are randomized data suggesting lower rates of MR-DWI abnormalities using transfemoral proximal protection.⁵⁷ Unfortunately, the WL Gore system is no longer manufactured or available. The Silk Road device, as mentioned previously, is surgically placed directly into the CCA so that arch manipulation is unnecessary (Figure 24.10). Because it is larger than the transfemoral

devices (10.5-Fr outer diameter, 8-Fr inner diameter) and has a specifically engineered side-arm tubing connections and large-bore venous return tubing, it has a high-flow capacity and therefore is able to be a flow-reversal system without the need to occlude the ECA separately.

Use of proximal protection devices delivered from the femoral access site generally require a 9-Fr sheath with a 6-Fr device lumen, and after balloon occlusion with the device is established, there is only a continuous carotid stump pressure reflective of intracerebral hemodynamics but not the usual continuous systemic intraarterial pressure available to monitor intraprocedural carotid body-mediated fluctuations in blood pressure. Some laboratories preferring not to rely on intermittent cuff pressure for monitoring purposes and upsize to a 10-Fr femoral access sheath so that systemic pressure can be monitored continuously through a separate transducer on the sheath side port.

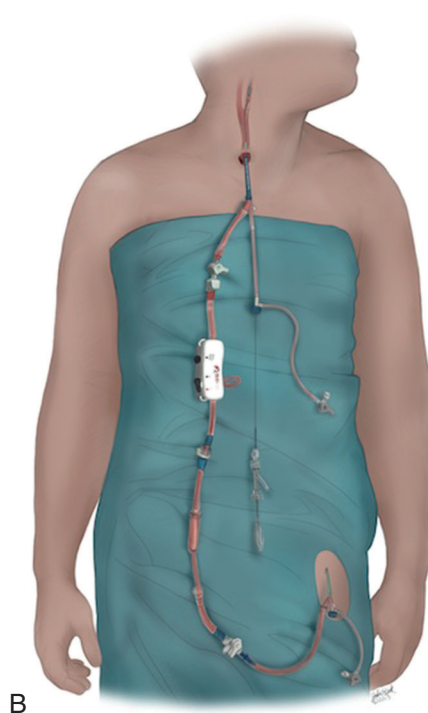
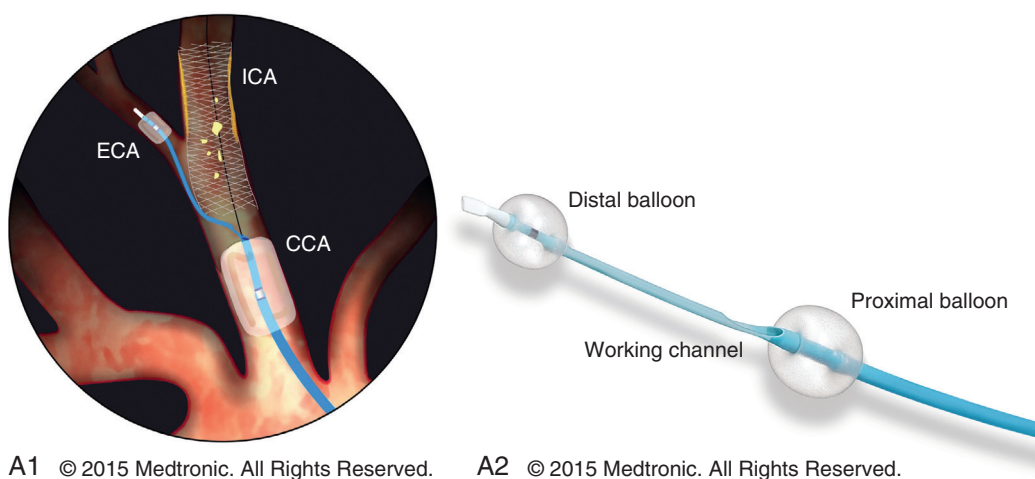


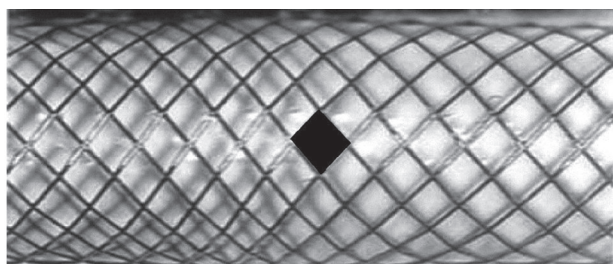
FIGURE 24.10 **A1**, Gore Flow Reversal System. **A2**, Medtronic Mo.Ma device. **B**, Silk Road Medical direct carotid access Michi system. CCA, Common carotid artery; ECA, external carotid artery; ICA, internal carotid artery. (**A**, © 2015 Medtronic. All Rights Reserved. **B**, From www.columbianeurosurgery.org/2013/09/meyers-sees-first-patients-in-roadster-trial/.)

Regardless of 9- or 10-Fr sheath sizing, preprocedural planning of access management and closure is an important component of successful procedure and involves the usual intersection of closure devices and anticoagulant strategies.

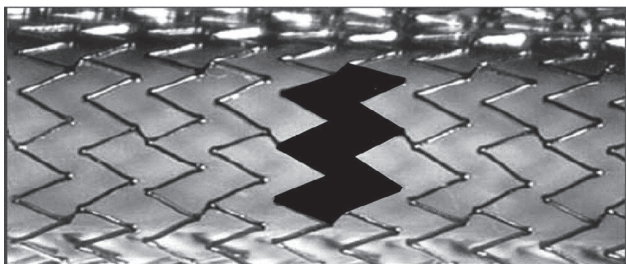
Later in this section, we discuss the predictors and management of neurologic and hemodynamic intraprocedural and postprocedural events, some of which are related to flow reversal or even cessation. In addition, the potential clinical differences between distal and proximal strategies in terms of the protection provided the patient are explored in later sections (Video 24.2).

Stent

Stent selection for CAS has been the topic of some debate and not a little controversy for nearly a decade and pivots on the concept that the stent is, in general, a provocative and not protective component of the procedure. This concept has been supported by imaging that has demonstrated plaque protrusion through stent struts after CAS.⁵⁸ Specifically, the openings between stent struts, termed *cells*, reduce the ability of the stent to completely trap the atherosclerotic material behind the metal structure. When discussing cells and carotid stents, definitions and terminology are important. All but one approved carotid stent is laser cut from a slotted tube of nitinol according to a preset pattern. Early, and some current, stent patterns had continuous connectors forming the cells, termed *closed cell*. This makes the stent stiff and nonconforming with the vessel wall, which is fine for reasonably straight vasculature but problematic in the tortuous anatomy, where it could impose significant vasculature kinking. To make these stents less rigid and more conformable, some of the connectors were removed, which created the “open-cell” stent (Figure 24.11). For the one woven carotid stent (Wallstent, Boston Scientific Corporation), which is made from Elgiloy (Co-Cr-Ni alloy), the cells are by definition



A



B

FIGURE 24.11 **A**, Closed-cell stent. **B**, Open-cell stents. The free cell areas are marked in black. (From Schillinger M, Gschwendtner M, Reimers B, et al. Does carotid stent cell design matter? *Stroke*. 2008;39:905-909.)

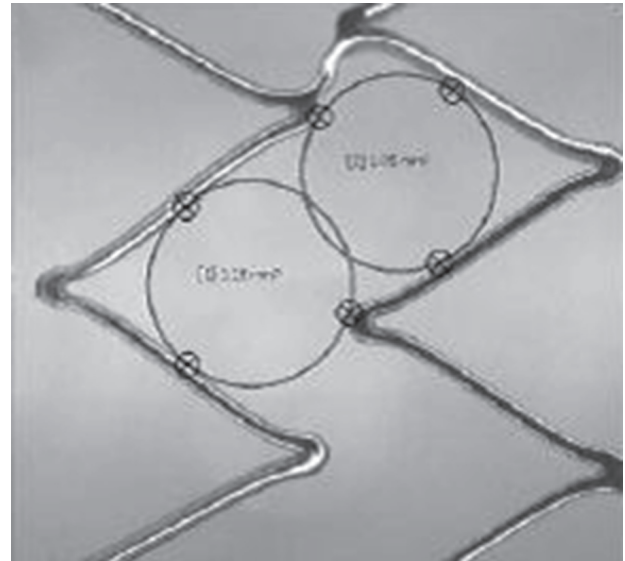


FIGURE 24.12 Illustration of maximal circular unsupported area or “largest fitted-in circle.” (Reused with permission from Müller-Hülsbeck S, Schäfer PJ, Charalambous N, et al. Comparison of carotid stents: an in-vitro experiment focusing on stent design. *J Endovasc Ther*. 2009;16:168-177.)

closed, albeit variable in size. Furthermore, there are two relevant terms used to describe the cells of a stent: free cell area and maximum circular unsupported surface area. The first term refers to the open area outlined by the stent struts, which will always be smaller for closed-cell stents (see Figure 24.11), and the second can be thought of as referring to the maximum size of a pellet that could fit through a cell (Figure 24.12), which in fact does not vary much according to cell type, the two measurements being only loosely related to each other (Figures 24.13 and 24.14). Many believe that the latter term is the more relevant measure of emboligenic potential.

Nevertheless, some practitioners have posited that closed-cell stent dimensions offer better trapping function of the stent and lessen the likelihood of an embolic complication causing stroke. Advocates of this view also point to data that appear to demonstrate a significant frequency of postprocedural stroke,⁴⁷ most of it in the first 24 hours, minor in severity, and nonhemorrhagic in nature, as support for a continued emboligenic hazard from the stent. To the contrary, transcranial Doppler monitoring of CAS after the procedure does not support continued embolization; in fact, no embolic signals are reported.⁵⁹ In addition, there are those who believe (this author included) that in fact, the “late” strokes that are noted are actually events that occur intraprocedurally but are either not detected or do not manifest until after the procedure. Giving credence to the first theory is the repeated observation that a neurologist will detect subtle strokes that the operators generally miss^{60,61} and this evaluation is typically done the day after the procedure, hence the late detection of the original procedural stroke. The second theory is at least in part supported by the practice of purposely allowing the patient’s blood pressure to become elevated by withholding medications on the day of the procedure to counter any vigorous carotid body-mediated hypotensive occurrence during the procedure. Medications are then reinstituted and

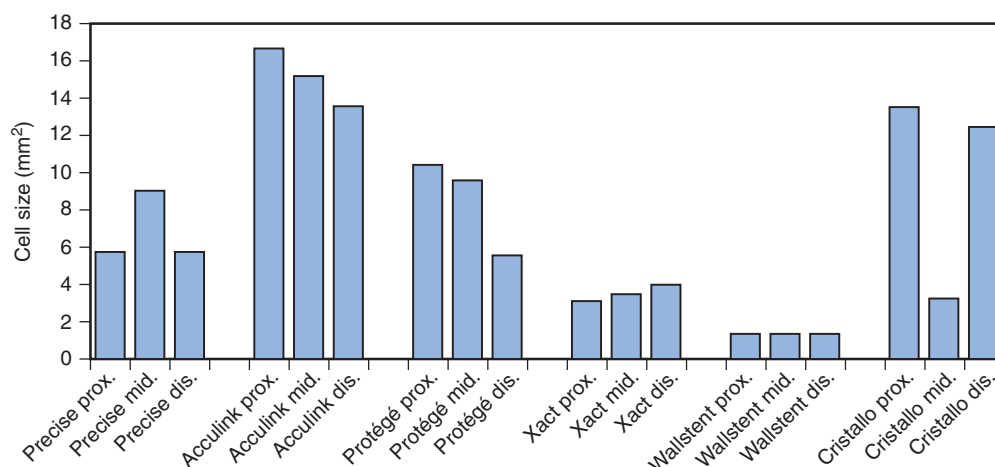


FIGURE 24.13 Relationship between free cell area. The Wallstent and the Xact stent are closed cell, and the Cristallo is a hybrid stent with open cells on the proximal (prox.) and distal (dist.) ends, with a closed cell design in the middle (mid.) part of the stent. (Redrawn with permission from Müller-Hülsbeck S, Schäfer PJ, Charalambous N, et al. Comparison of carotid stents: an in-vitro experiment focusing on stent design. *J Endovasc Ther.* 2009;16:168-177.)

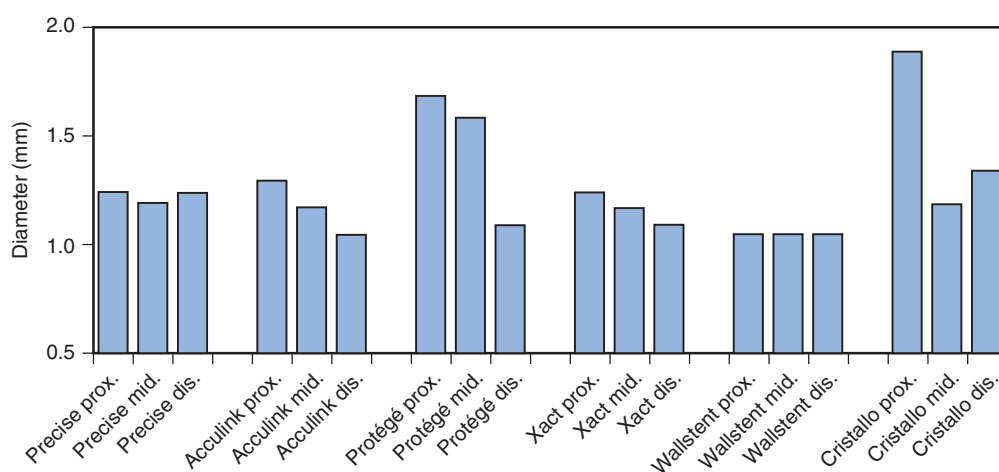


FIGURE 24.14 The characterization of carotid stents by their largest fitted-in circle demonstrating minimal differences among most of them. Note that the Cristallo stent is not approved for use in the United States. Dist., Distal; mid., middle; prox., proximal. (Redrawn with permission from Müller-Hülsbeck S, Schäfer PJ, Charalambous N, et al. Comparison of carotid stents: an in-vitro experiment focusing on stent design. *J Endovasc Ther.* 2009;16:168-177.)

blood pressure controlled; if a minor event occurs intraprocedurally, the permissive hypertension could mask it by increasing collateralization, only to become evident when the collateral flow is reduced as blood pressure normalizes. This phenomenon has been documented to occur and is therefore also a tenable explanation for delayed notification of stroke after CAS.⁶²

Moreover, definitive comparative clinical data supporting a differential outcome effect of stent type is lacking. Remember that to demonstrate any material clinical differences in the already low CAS event rates would require several thousand prospectively randomized patients, and all the data—on both sides of the argument—generally fall far short. One of the first reports was from Bosiers et al.,⁶³ who retrospectively analyzed more than 3000 patients from four interventional sites in Europe and found worse outcomes according to free cell area among symptomatic, but not asymptomatic, patients. However, this analysis was not propensity adjusted and was therefore subject to significant selection bias. Moreover, the vast majority of closed-cell stents were Wallstents, which were more than

two-thirds of the stents used, of a total of seven stent types. This disproportionate use of one stent type has several implications, including small sample sizes in the remaining stent groups and that no statement regarding class effect related to cell type can legitimately be made. There have been several other retrospective studies, some propensity adjusted, that have not shown any differences in outcomes by stent type.^{64,65} Last, the most voluminous and least biased by selection or ascertainment are the data from the high surgical risk single-arm contemporaneously run prospective post-market US studies, CAPTURE 2 and EXACT, which demonstrated no outcome differences between the closed-cell Xact and the open-cell Acculink stents.¹⁵

The observations that even the smallest cell area in current stents are a relatively large 2 mm² have led to the development of mesh-covered open-cell stents. In this manner, the flexibility of an open-cell stent can be combined with maximal plaque coverage: the mesh “cell size” is in the 0.25-mm² range. Possible trade-offs to this approach include the potential for an increase in stent thrombosis

(a rare event with current stents) or possible changes in long-term stent patency. The SCAFFOLD trial by WL Gore tested such a stent, and in the single-arm multicenter core-lab controlled study in high surgical risk patients, the results were promising with low rates of 30-day stroke (1.1%) and clinically driven target lesion revascularization of 1.6% at 1 year.⁶⁶ Unfortunately, despite these very competitive results, because business—and not clinical—considerations, this device has not been commercialized. Another version of a mesh-covered stent called the CGUARD (InspireMD) has shown promise both in a small 30-participant clinical trial (no strokes at 3 days) but also in an apparent reduction in both count and volume of new asymptomatic postprocedure MR-DWI abnormalities compared with historical references, suggesting a possible mechanistic advantage of the mesh as a cerebral protectant strategy.⁶⁷ With the pivotal US trial of this device currently enrolling, the ultimate place of mesh-covered stents is still to be determined.

Other selection decisions related to the stent involve tapered versus straight shapes, without data to differentiate outcomes, and stent length that ranges from 2 to 4 cm. All current stents fit through a 6-Fr sheath, a minority through a 5-Fr sheath. After the stent has been selected, the technical aspects of stent implantation are relatively straightforward. The lesion is generally centered within the chosen stent length to provide a reasonably disease-free zone 0.5 to 1.0 cm at the proximal and distal margins. In most cases, except in post-CEA restenosis, the lesion will involve the carotid bifurcation because the flow eddy there promotes the lesion in the first place even if the most severe aspect of the lesion is more distal; therefore, every effort should be made to cover the bifurcation with the stent to assure that the potential for plaque rupture there is reduced as well. If there is significant tortuosity in the vessel, an open-cell stent will provide for much less vessel kinking after deployment and is typically chosen. Stent localization in an angulated or tortuous vessel is done so as not to accentuate the straightening effect, which can lead to vessel kinking, even by a more flexible open-cell stent, by not placing the edge of the stent at the junction of a straight and turned segment. Finally, there does not appear to be a penalty for stent length in terms of acute thrombosis or long-term patency, so longer stents (≤ 4 cm) are generally chosen to assure lesion coverage and minimize geographic miss.

Balloon Dilation

Although individual operators have stylistic differences, balloon dilation during CAS is generally done both before (predilation) and after (postdilation) stent implantation. Predilation balloons are generally undersized (2–4 mm) and longer (3–4 cm) than the lesion so as to minimize balloon slippage. Given that the average human mid-distal ICA ranges between 5.0 and 5.5 cm and the CCA and carotid bulb are always larger, the undersized predilation balloon will only interact with the lesion and not the remaining vessel so no unintended vessel trauma is inflicted. Some operators have used specialty balloons (e.g., cutting, scoring) in calcified lesions, but no data support this practice, and the risk of carotid perforation—rare

in CAS—may be increased. However, there may be reasonable logic supported by reports of safety and early efficacy to use these specialty balloons to treat in-stent restenosis.⁶⁸⁻⁷⁰ Postdilation balloons are usually not sized bigger than 5.0 mm in diameter and 2 cm in length because anything larger is unnecessary to achieve stenosis resolution (residual $<30\%$) given the aforementioned standard ICA size and can potentially create more emboligenic risk.

There have been modifications to the predilation and postdilation algorithm, each with its own logic but neither with much data support. Some operators choose not to predilate the lesion, preferring instead to primarily place the stent and then postdilate. This is considered time saving and so reduces filter dwell, or flow-reversal or cessation, time. Others, including this operator, prefer to fully predilate with a 4.0-mm balloon, then stent, and assess for the need to postdilation. A residual stenosis of less than 30% is generally not postdilated and occurs in roughly half of the cases we perform. The rationales for this approach are the following:

- Predilation is generally not associated with clinical or angiographic complication.
- There are no convincing data that a minor residual stenosis after CAS leads to worse acute or long-term outcomes and that the 4.0-mm balloon is likely to produce an adequate, stand-alone CAS result in resistant lesions.
- Most of the anecdotal reports of the occurrence of intraprocedural stroke are during the postdilation phase.
- Transcranial microembolic signal patterns confirm that postdilation is the most emboligenic part of the CAS procedure (apart from the stent placement, which is likely related to microbubbles trapped in the stent sheath and released while retracting the sheath during stent deployment).⁷¹
- When hemodynamic compromise occurs in CAS, it is usually the result of postdilation.

There may be other reasons to perform postdilation beyond reducing residual stenosis, including difficulty in passing the retrieval catheter for the filter, which can be caused by stent struts in an open-cell stent that have not “laid down” or a leading edge of any stent that needs to be better opposed to the vessel wall. Of course, hemodynamic perturbations already extant after stent placement will also modify any postdilation strategy.

Hemodynamic Management

Carotid artery stenting can produce both bradycardia and hypotension via stimulation of the carotid sinus by balloon dilation, stent implantation, or both. The bradycardia is a usually short-lived, vagal-mediated, parasympathetic response that typically resolves with balloon depressurization or deflation; it can typically be managed with atropine, and long-term increase in permanent pacemaker placement is not reported. The placement of a prophylactic temporary pacemaker is occasionally warranted in patients with critical aortic stenosis or severe cardiomyopathy with residual nonrevascularized ischemic coronary lesions because in neither type of patient is loss of coronary circulation tolerated and may be irrecoverable.

Alternatively, hypotension is mediated through a sympathetic medullary pathway that can result in profound

venodilation that, with or without accompanying bradycardia, can cause a significant and dramatic drop in blood pressure. Depending on the definition used, the incidence of significant hypotension is usually defined as the need for prolonged pressor support ranging from 14% to 51%.⁷²⁻⁷⁷ Although previously thought to be a benign procedural occurrence if managed promptly, newer data suggest that it may be associated with an increased number of new lesions on MR-DWI.⁷⁸ Patients with bulky, calcified lesions involving the carotid bulb are thought to be at most risk of developing procedural hypotension,⁷⁹ and this may in fact be a confounding feature as regards the finding of MR-DWI lesions.

Procedural hypotension is best managed before it starts by withholding antihypertensive medications on the morning of the procedure. This, along with patient anxiety, typically results in preprocedural blood pressures greater than 160 mm, and it is important to resist treating the hypertension acutely because precipitous decreases in systolic blood pressure of up to 80 to 100 mm can occur within seconds of dilation or stent placement. Another preventive strategy is to make certain that the patient is not dehydrated (given the venodilatory mechanism described previously), which can often be the case because patients have been nothing by mouth for several hours or overnight before CAS. In most cases, the patient will tolerate at least a 250- to 500-cc intravenous (IV) bolus preprocedure, and it is our custom to do so.

When the patient becomes hypotensive, preparation and rapid action are key. Nursing staff should be serviced as to all potential consequences of CAS, medication should be drawn and ready for administration, and a well-functioning IV should be ensured. A check of nursing preparedness before postdilation balloon inflation is always a good idea. Atropine and Neo-Synephrine injectables are typical acute treatment choices, and dopamine drip (which can address both bradycardia and hypotension) should be mixed and ready as needed. Rapid administration of normal saline or lactated Ringer's solution is an important component of treatment as well. The procedural hypotension should be able to be recovered within 1 to 2 minutes, at least temporarily (prolonged pressor drips are occasionally required), and the operator will need to consider whether any further procedural steps are required to complete the CAS and wrap up in an expeditious fashion. Other causes of hypotension (e.g., access site hemorrhage) should always be kept in mind as well. The hypotension related to CAS can be considered an acquired autonomic dysfunction, and for this reason, many operators prefer to use a closure device for the access site whenever possible and push for early ambulation—even if some pressor support is present or required—because prolonged bedrest can extend the time of the hypotensive period.

As problematic as procedural bradycardia and hypotension can be, the persistence of hypertension after carotid revascularization can be equally important and needs to be managed appropriately and aggressively. Hypertension may persist for a variety of reasons, including prior CEA, which denervates the carotid body and largely obviates any response, a primary lesion location away from

the bulb, variability in lesion responsiveness, and so on. Regardless, the hypertension should be quickly brought under control because it is believed to be a contributor to cerebral hemorrhage, especially in isolated vascular territories (i.e., poorly collateralized) or recently or repetitively symptomatic patients. In addition to reinstituting the preprocedural antihypertensive medication regimen, many laboratories temporize using IV beta-blockers as heart rate allows and IV nitroglycerin (NTG) for immediate hypertension control. However, longer term administration of NTG can be problematic owing not only to rapid tachyphylaxis but also the side effect of headache, which can be confusing as intracranial hemorrhage, is a concern in this at-risk population, and may be difficult to distinguish. Many operators prefer an IV calcium channel blocker (e.g., nifedipine) as first-line management of blood pressure, which provides predictable control but is not associated with confounding symptomatic side effects.

Neurologic Management

This section is dedicated to the management of neurologic changes when they occur as part of the procedure. The patient undergoing CAS can have neurologic symptoms for a variety of reasons, and rapid diagnosis can be important in the correct management. The majority of neurologic symptoms are related to a proximal or embolic slowing or interruption of flow, causing hypoperfusion and cerebral ischemia. Before addressing the management of these more common presentations, it is worth noting that although quite infrequent, some patients with isolated cerebral circulation caused by an incomplete circle of Willis have a partial or generalized seizure when even a short predilation balloon inflation interrupts blood flow, with focal symptoms persisting after flow restoration because of a Todd's paralysis, giving the impression of possible embolic complication.

When using proximal protection of any variety, antegrade flow is purposefully interrupted or reversed. Mean stump pressure readings above 40 mm Hg are usually sufficient to maintain cerebral perfusion. However, symptoms of intolerance may be seen at pressures lower than 30 to 40 mm Hg. Subtle symptoms include slowness to respond to commands or questions, yawning, agitation, or lowered level of consciousness. More overt symptoms may include focal neurologic signs, generalized seizures, or loss of consciousness. A high index of suspicion can allow the operator to reduce or eliminate symptoms of intolerance. If systemic blood pressure is raised, then cerebral collateral perfusion can be further recruited or enabled and should be one of the first maneuvers attempted in low-grade intolerance. If this maneuver is not successful in mitigating symptoms or if they worsen, then releasing the proximal CCA balloon occlusion and restoring flow are indicated but only after the column of blood (in the case of flow cessation) is cleared of any debris via aspiration. It is possible in some patients to precondition the cerebral circulation with intermittent occlusion such that successively longer interruptions in flow can be tolerated. In most cases, the procedure can be completed in less than 5 minutes with good preparation, so usually intolerance is not an issue in CAS except in the most extreme cases. In cases of absolute intolerance, a filter EPD can be deployed through the

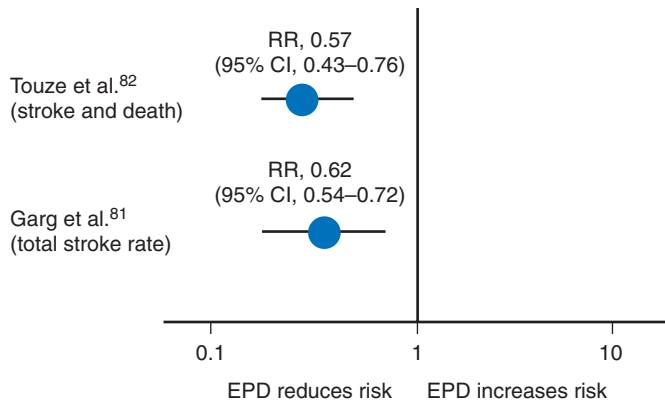


FIGURE 24.15 Results of summary data from meta-analyses of the clinical utility of embolic protection device (EPD) use in carotid artery stenting. CI, Confidence interval; RR, relative risk. (Redrawn with permission from White CJ. Carotid artery stenting. *J Am Coll Cardiol*. 2014;64:722-731.)

proximal protection sheath system and the protected procedure completed this way. A corollary cause of neurologic symptoms can occur when a no-flow situation arises because of a filter that has become occluded with debris, fibrin, or both. In these cases, it is especially important to suction and clear the static column of blood below the filter because it almost certainly contains meaningful and harmful debris.

Although no randomized studies have proven the efficacy of EPDs in preventing stroke, both anecdotal experience and meta-analyses suggest that they are indeed protective, almost certainly for major embolic complications, with very little downside risk⁸⁰⁻⁸² (Figure 24.15). These observations are counterposed with nonclinical imaging data suggesting that there are greater numbers of asymptomatic MR-DWI abnormalities with the use of filters, possibly related to the embolization of microbubbles released when the sheath is withdrawn to deploy the filter.⁸³ Nevertheless, embolic complications can still occur when loss of filtration occurs because of a lack of wall opposition (e.g., when a filter is positioned on a vessel bend point) or after the filter is removed as discussed previously. Intraprocedural embolic complications can manifest immediately as a focal sign or may be masked by the permissive hypertension associated with CAS as mentioned previously. However, if immediate symptoms arise and are confirmed by angiography to be due to embolism, a relatively straightforward decision tree can be followed. Armed with the knowledge that most minor strokes, defined as a change in the NIHSS of less than 4, resolve within 30 days with little or no disability, then the site of embolic occlusion can be managed appropriately.^{12,22} A proximal intracranial vessel occlusion generally produces major stroke symptoms and requires immediate neurointerventional management and extraction of the offending material. However, more distal occlusions (M3 or M4) are more likely (but not always) associated with lesser symptomatology that is also likely to largely resolve, and because their retrieval can be problematic and potentially risky, the decision to attempt intracranial manipulations is generally tempered. The role of pharmacological treatment with intraarterial or systemic thrombolytics or glycoprotein IIb/IIIa platelet inhibitors

has not been defined in distal embolization after CAS associated with a neurologic syndrome, but intracranial bleeding has been associated with the latter's use, so it is generally avoided.

Pharmacology

Although there are no data to drive pre- and postprocedural pharmacology, the accepted standard is to initiate dual antiplatelet therapy (DAPT) with clopidogrel and aspirin at least 3 days ahead of the procedure or to give a loading dose of clopidogrel several hours ahead of the procedure. DAPT is continued for 30 days, although shorter durations (~2 weeks) have been used in cases in which the need for early cardiac surgery was present. The carotid artery is a high-flow vessel supplying a low-resistance cerebral circulation, and the medium-diameter stents used for CAS rarely thrombose; when they do, it generally occurs acutely at the time of implant and is thought to be related to the biology of the plaque (i.e., intraplaque contents), although the inadequacy of pharmacology has also been suggested.^{84,85} Intraprocedural anticoagulation is also not driven by data but more by convention, with recommended activated clotting times longer than 250 to 300 seconds, with the most susceptible component of the procedure to inadequate anticoagulation is likely the filter. Anticoagulation can be achieved using either heparin or bivalirudin. Prior smaller, single-center, and nonrandomized data support that the use of bivalirudin appears to be at least as safe as heparin.⁸⁶

CONCLUSIONS

Carotid artery stenting is a relatively young interventional field, having been practiced with dedicated approved equipment for nearly 2 decades, although it has been under a restricted US coverage and reimbursement environment. Nevertheless, a great deal of improvement in outcomes has been documented, most likely related to the accumulated knowledge regarding technique and patient selection. Future directions will include efforts to reduce nonclinical but likely meaningful surrogates such as MR-DWI with improvements in stent construction, access techniques and sites, and EPD strategies. These improvements will almost certainly accrue to the benefit of our patients.

REFERENCES

1. Bockenheimer SA, Mathias K. Percutaneous transluminal angioplasty in arteriosclerotic internal carotid artery stenosis. *AJNR Am J Neuroradiol*. 1983;4(3):791-792.
2. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet*. 2001;357(9270):1729-1737.
3. North American Symptomatic Carotid Endarterectomy Trial Collaborators: beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445-453.
4. Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*. 2006;355(16):1660-1671.
5. SPACE Collaborative Group, Ringleb PA, Allenberg J, et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet*. 2006;368(9543):1239-1247.
6. International Carotid Stenting Study investigators, Ederle J, Dobson J, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet*. 2010;375(9719):985-997.

7. Stulp E, Baird C, Gray WA, et al. An evidence-based review of the impact of periprocedural myocardial infarction in carotid revascularization. *Catheter Cardiovasc Interv.* 2013;82(5):709-714.
8. Diethrich EB, Ndiaye M, Reid DB. Stenting in the carotid artery: initial experience in 110 patients. *J Endovasc Surg.* 1996;3(1):42-62.
9. Yadav JS, Roubin GS, Iyer S, et al. Elective stenting of the extracranial carotid arteries. *Circulation.* 1997;95(2):376-381.
10. Alberts MJ. Results of a multicenter prospective randomized trial of carotid artery stenting vs carotid endarterectomy. *Stroke.* 2001;32:325.
11. Yadav JS, Wholey MH, Kuntz RE, et al. Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy investigators: protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med.* 2004;351(15):1493-1501.
12. Gray WA, Hopkins LN, Yadav S, et al. Protected carotid stenting in high surgical-risk patients: the ARChEr results. *J Vasc Surg.* 2006;44(2):258-268.
13. Gray WA, Yadav JS, Verta P, et al. The CAPTURE registry: results of carotid stenting with embolic protection in the post approval setting. *Catheter Cardiovasc Interv.* 2007;69(3):341-348.
14. Gray WA, Rosenfield KA, Jaff MR, et al. Influence of site and operator characteristics on carotid artery stent outcomes: analysis of the CAPTURE 2 (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events) clinical study. *JACC Cardiovasc Interv.* 2011;4(2):235-246.
15. Gray WA, Chaturvedi S, Verta P, et al. Thirty-day outcomes for carotid artery stenting in 6320 patients from 2 prospective, multicenter, high surgical-risk registries. *Circ Cardiovasc Interv.* 2009;2(3):159-166.
16. Massop D, Dave R, Metzger C, et al. Stenting and angioplasty with protection in patients at high-risk for endarterectomy: SAPHIRE Worldwide Registry first 2,001 patients. *Catheter Cardiovasc Interv.* 2009;73(2):129-136.
17. Shishehbor MH, Venkatachalam S, Gray WA, et al. Experience and outcomes with carotid artery stenting: an analysis of the CHOICE (Carotid Stenting for High Surgical-Risk Patients; evaluating outcomes through the collection of clinical evidence) study. *JACC Cardiovasc Interv.* 2014;7(11):1307-1317.
18. Brott TG, Hobson RW II, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med.* 2010;363(1):11-23.
19. Hobson RW II, Howard VJ, Roubin GS, et al. Credentialing of surgeons as interventionalists for carotid artery stenting: experience from the lead-in phase of CREST. *J Vasc Surg.* 2004;40(5):952-957.
20. Eckstein H-H, Ringleb P, Allenberg J-R, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol.* 2008;7(10):893-902.
21. Mas JL, Trinquart L, Leys D, et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol.* 2008;7(10):885-892.
22. Gray WA, Simonton CA, Verta P. Overview of the 2011 Food and Drug Administration circulatory system devices panel meeting on the ACCULINK and ACCUNET carotid artery stent system. *Circulation.* 2012;125(18):2256-2264.
23. Gensicke H, Zumbunn T, Jongen LM, ICSS-MRI Substudy Investigators. Characteristics of ischemic brain lesions after stenting or endarterectomy for symptomatic carotid artery stenosis: results from the International Carotid Stenting Study-magnetic resonance imaging substudy. *Stroke.* 2013;44(1):80-86.
24. Chen CI, Iguchi Y, Garami Z, et al. Analysis of emboli during carotid stenting with distal protection device. *Cerebrovasc Dis.* 2006;21(4):223-228.
25. Rosenfield K, Matsumura JS, Chaturvedi S, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. *N Engl J Med.* 2016;374(11):1011-1020.
26. Halliday A, Bulbulia R, Bonati LH, et al. Second asymptomatic carotid surgery trial (ACST-2): a randomised comparison of carotid artery stenting versus carotid endarterectomy. *Lancet.* 2021;398(10305):1065-1073.
27. Rostamzadeh A, Zumbunn T, Jongen LM, et al. Predictors of acute and persisting ischemic brain lesions in patients randomized to carotid stenting or endarterectomy; ICSS-MRI Substudy Investigators. *Stroke.* 2014;45(2):591-594.
28. Gaudet JG, Meyers PM, McKinsey JF, et al. Incidence of moderate to severe cognitive dysfunction in patients treated with carotid artery stenting. *Neurosurgery.* 2009;65(2):325-329.
29. Plessers M, Van Herzele I, Vermassen F, et al. Neurocognitive functioning after carotid revascularization: a systematic review. *Cerebrovasc Dis Extra.* 2014;4(2):132-148.
30. Eastcott H. Reconstruction of internal carotid artery in a patient with intermittent attacks of hemiplegia. *Lancet.* 1954;264:994-996.
31. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA.* 1995;273:1421-1428.
32. Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet.* 2004;363(9420):1491-1502.
33. Halliday A, Harrison M, Hayter E, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet.* 2010;376(9746):1074-1084.
34. Henderson RD, Eliasziw M, Fox AJ, et al. Angiographically defined collateral circulation and risk of stroke in patients with severe carotid artery stenosis. *Stroke.* 2000;31(1):128-132.
35. Ku DN, Giddens DP, Zarins CK, et al. Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress. *Arteriosclerosis.* 1985;5:293-302.
36. Ouriel K, Green RM. Clinical and technical factors influencing recurrent carotid stenosis and occlusion after endarterectomy. *J Vasc Surg.* 1987;5(5):702-706.
37. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery Developed in Collaboration With the American Academy of Neurology and Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol.* 2011;57:1002-1044.
38. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and to the timing of surgery. *Lancet.* 2004;363:915-924.
39. Barnett HJM, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in symptomatic patients with moderate and severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med.* 1998;339:1415-1425.
40. Matsumura JS, Gray W, Chaturvedi S, et al. Results of carotid artery stenting with distal embolic protection with improved systems: protected carotid artery stenting in patients at high risk for carotid endarterectomy (PROTECT) trial. *J Vasc Surg.* 2012;55(4):968-976.
41. Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. *Stroke.* 2009;40(10):e573-e583.
42. Marquardt L, Geraghty OC, Mehta Z, et al. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment. *Stroke.* 2010;41(1):e11-e17.
43. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet.* 1998;351:1379-1387.
44. Moneta GL, Edwards JM, Chitwood RW, et al. Correlation of North American Symptomatic Carotid Endarterectomy Trial (NASCET) angiographic definition of 70% to 99% internal carotid artery stenosis with duplex scanning. *J Vasc Surg.* 1993;17(1):152-157.
45. Gray WA, Yadav JS, Verta P, et al. The CAPTURE registry: predictors of outcomes in carotid artery stenting with embolic protection for high surgical risk patients in the early post-approval setting. *Catheter Cardiovasc Interv.* 2007;70(7):1025-1033.
46. Etgegoien N, Rhyne D, Kedev S, et al. The transradial approach for carotid artery stenting. *Catheter Cardiovasc Interv.* 2012;80(7):1081-1087.
47. Fairman R, Gray WA, Scicli AP, et al. The CAPTURE registry: analysis of strokes resulting from carotid artery stenting in the post approval setting: timing, location, severity, and type. *Ann Surg.* 2007;246(4):551-556.
48. Leal I, Orgaz A, Flores A, et al. A diffusion-weighted magnetic resonance imaging-based study of transcervical carotid stenting with flow reversal versus transfemoral filter protection. *J Vasc Surg.* 2012;56(6):1585-1590.
49. Galyfos GC, Tsoutsas I, Konstantopoulos T, et al. Early and late outcomes after transcarotid revascularisation for internal carotid artery stenosis: a systematic review and meta-analysis. *Eur J Vasc Endovasc Surg.* 2021;61(5):725-738.
50. Paraskevas KI, Antonopoulos CN, Kakisis JD, Geroulakos G. An updated systematic review and meta-analysis of results of transcervical carotid artery stenting with flow reversal. *J Vasc Surg.* 2020;72(4):1489-1498.e1.
51. Lohmanpour NA, Siewiorek GM, Wanamaker KM, et al. Assessing the impact of distal protection filter design characteristics on 30-day outcomes of carotid artery stenting procedures. *J Vasc Surg.* 2013;57(2):309-317.
52. Langhoff R, Schofer J, Scheinert D, et al. Double filtration during carotid artery stenting using a novel post-dilation balloon with integrated embolic protection. *JACC Cardiovasc Interv.* 2019;12(4):395-403.
53. Clair DG, Hopkins LN, Mehta M, et al. Neuroprotection during carotid artery stenting using the GORE flow reversal system: 30-day outcomes in the EMPiRE Clinical Study. *Catheter Cardiovasc Interv.* 2011;77(3):420-429.
54. Ansel GM, Hopkins LN, Jaff MR, et al. Safety and effectiveness of the INVATEC MO.MA proximal cerebral protection device during carotid artery stenting: results from the ARMOUR pivotal trial. *Catheter Cardiovasc Interv.* 2010;76(1):1-8.
55. Bersin RM, Stabile E, Ansel GM, et al. A meta-analysis of proximal occlusion device outcomes in carotid artery stenting. *Catheter Cardiovasc Interv.* 2012;80(7):1072-1078.
56. Matsumura JS, Gray W, Chaturvedi S, et al. Results of carotid artery stenting with distal embolic protection with improved systems: protected carotid artery stenting in patients at high risk for carotid endarterectomy (PROTECT) trial. *J Vasc Surg.* 2012;55(4):968-976.
57. Montorsi P, Caputi L, Galli S, et al. Microembolization during carotid artery stenting in patients with high-risk, lipid-rich plaque. A randomized trial of proximal versus distal cerebral protection. *J Am Coll Cardiol.* 2011;58(16):1656-1663.
58. de Donato G, Setacci F, Sirignano P, et al. Optical coherence tomography after carotid stenting: rate of stent malapposition, plaque prolapse and fibrous cap rupture according to stent design. *Eur J Vasc Endovasc Surg.* 2013;45(6):579-587.

59. Censori B, Camerlingo M, Casto L, et al. Carotid stents are not a source of microemboli late after deployment. *Acta Neurol Scand.* 2000;102(1):27-30.
60. Rothwell PM, Slattery J, Warlow CP. A systematic review of the risks of stroke and death due to endarterectomy for symptomatic carotid stenosis. *Stroke.* 1996;27(2):260-265.
61. Chaturvedi S, Aggarwal R, Murugappan A. Results of carotid endarterectomy with prospective neurologist follow-up. *Neurology.* 2000;55(6):769-772.
62. Tan KT, Cleveland TJ, Berczi V, et al. Timing and frequency of complications after carotid artery stenting: what is the optimal period of observation? *J Vasc Surg.* 2003;38(2):236-243.
63. Bosiers M, de Donato G, Deloose K, et al. Does free cell area influence the outcome in carotid artery stenting? *Eur J Vasc Endovasc Surg.* 2007;33(2):135-141.
64. Schillinger M, Gschwendtner M, Reimers B, et al. Does carotid stent cell design matter? *Stroke.* 2008;39(3):905-909.
65. Grunwald IQ, Reith W, Karp K, et al. Comparison of stent free cell area and cerebral lesions after unprotected carotid artery stent placement. *Eur J Vasc Endovasc Surg.* 2012;43(1):10-14.
66. Gray WA, Levy E, Bacharach JM, et al. Evaluation of a novel mesh-covered stent for treatment of carotid stenosis in patients at high risk for endarterectomy: 1-year results of the SCAFFOLD trial. *Catheter Cardiovasc Interv.* 2020;96(1):121-127.
67. Schofer J, Musialek P, Bijuklic K, et al. A prospective, multicenter study of a novel mesh-covered carotid stent: the CGuard CARENET trial (Carotid Embolic Protection Using MicroNet). *JACC Cardiovasc Interv.* 2015;8(9):1229-1234.
68. Bendok BR, Roubin GS, Katzen BT, et al. Cutting balloon to treat carotid in-stent stenosis: technical note. *J Invasive Cardiol.* 2003;15:227-232.
69. Tamberella MR, Yadav JS, Bajzer CT, et al. Cutting balloon angioplasty to treat carotid in-stent stenosis. *J Invasive Cardiol.* 2004;16:133-135.
70. Shah QA, Georgiadis AL, Suri MF, et al. Cutting balloon angioplasty for carotid in-stent restenosis: case reports and review of the literature. *J Neuroimaging.* 2008;18:428-432.
71. Antonius Carotid Endarterectomy, Angioplasty and Stenting Study Group: transcranial Doppler monitoring in angioplasty and stenting of the carotid bifurcation. *J Endovasc Ther.* 2003;10(4):702-710.
72. Dangas G, Laird JR Jr, Satler LF, et al. Postprocedural hypotension after carotid artery stent placement: predictors and short- and long-term clinical outcomes. *Radiology.* 2000;215:677-683.
73. Gupta R, Abou-Chebl A, Bajzer CT, et al. Rate, predictors, and consequences of depression after carotid artery stenting. *J Am Coll Cardiol.* 2006;47:1538-1543.
74. Park BD, Divinagracia T, Madej O, et al. Predictors of clinically significant postprocedural hypotension after carotid endarterectomy and carotid angioplasty with stenting. *J Vasc Surg.* 2009;50:526-533.
75. Qureshi AI, Luft AR, Sharma M, et al. Frequency and determinants of post-procedural hemodynamic instability after carotid angioplasty and stenting. *Stroke.* 1999;30:2086-2093.
76. Lavoie P, Rutledge J, Dawoud MA, et al. Predictors and timing of hypotension and bradycardia after carotid artery stenting. *AJNR Am J Neuroradiol.* 2008;29:1942-1947.
77. Altinbas A, Algra A, Bonati LH, et al. Periprocedural hemodynamic depression is associated with a higher number of new ischemic brain lesions after stenting in the International Carotid Stenting Study-MRI Substudy. *Stroke.* 2014;45(1):146-151.
78. Matsukawa H, Fujii M, Uemura A, et al. Pathology of embolic debris in carotid artery stenting. *Acta Neurol Scand.* 2015;131(4):197-202.
79. Gupta R, Abou-Chebl A, Bajzer CT, et al. Rate, predictors, and consequences of hemodynamic depression after carotid artery stenting. *J Am Coll Cardiol.* 2006;47(8):1538-1543.
80. Macdonald S. The evidence for cerebral protection: an analysis and summary of the literature. *Eur J Radiol.* 2006;60(1):20-25.
81. Garg N, Karagiorgos N, Pisimisis GT, et al. Cerebral protection devices reduce periprocedural strokes during carotid angioplasty and stenting: a systematic review of the current literature. *J Endovasc Ther.* 2009;16:412-427.
82. Touzé E, Trinquart L, Chatellier G, et al. Systematic review of the perioperative risks of stroke or death after carotid angioplasty and stenting. *Stroke.* 2009;40:e683-e693.
83. Macdonald S, Evans DH, Griffiths PD, et al. Filter-protected versus unprotected carotid artery stenting: a randomised trial. *Cerebrovasc Dis.* 2010;29(3):282-289.
84. Xiomeritis K, Dalainas I, Stamatakis M, et al. Acute carotid stent thrombosis after carotid artery stenting. *Eur Rev Med Pharmacol Sci.* 2012;16(3):355-362.
85. Köklü E, Arslan S, Yüksel IO, et al. Acute carotid artery stent thrombosis due to dual antiplatelet resistance. *Cardiovasc Intervent Radiol.* 2015;38(4):1011-1014.
86. Schneider LM, Polena S, Roubin G, et al. Carotid stenting and bivalirudin with and without vascular closure: 3-year analysis of procedural outcomes. *Catheter Cardiovasc Interv.* 2010;75(3):420-426.



25

Cerebrovascular Interventions

ALEX BOU CHEBL

INTRODUCTION, 462

Cerebrovascular Disease, 462

THE CEREBRAL VASCULATURE, 463

ACUTE ISCHEMIC STROKE TREATMENT, 465

Indications and Contraindications, 465

Techniques, 465

Clinical Outcomes, 470

Intracranial Angioplasty and Stenting, 471

Indications and Patient Selection, 472

Clinical Manifestations, 472

Techniques, 472

Clinical Outcomes, 475

CONCLUSIONS, 476

INTRODUCTION

Percutaneous techniques for the treatment of patients with cerebrovascular diseases have evolved quickly since the previous edition of this chapter was written. Importantly, there has also been a wealth of new clinical evidence supporting the use of these techniques for the management of cerebrovascular diseases, acute ischemic stroke (AIS) in particular. Despite these advances, many challenges and risks remain primarily because of the tortuosity and fragility of the cerebral vasculature.

Cerebrovascular Disease

Epidemiology

In the United States, approximately 800,000 new strokes occur annually.¹ Stroke mortality rates have been decreasing, and stroke is currently the fifth leading cause of death in the United States, although it continues to be the leading cause of disability in US adults.¹

The majority of strokes are ischemic (85%), and the minority are hemorrhagic.^{2,3} The pathophysiology of ischemic stroke is highly varied, unlike acute coronary syndrome or ST-segment elevation myocardial infarction (STEMI). The most common (~30%) cause of AIS is lacunar disease (i.e., lipohyalinosis affecting the small perforating arteries at the base of the brain stroke, which are not currently amenable to endovascular therapy [EVT]). The remainder of AIS cases involve the large cerebral arteries, but the underlying pathologies are highly varied. Cardiac embolism causes 20% of AISs, and large vessel atherosclerosis is responsible for another 20%. About 25% are of unknown cause, and the remaining 5% are caused by arterial dissection (in young individuals), hypercoagulability, inflammatory disorders, and metabolic and genetic conditions.^{4,5} Hemorrhagic strokes consist mostly (85%) of intracranial hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Although the management of these conditions is not the aim of this chapter, the fact that AIS management can lead to ICH and SAH and vice versa necessitates a rudimentary discussion of their manifestations and management.

As to be expected, stroke (ischemic and hemorrhagic) risk factors are the usual risk factors associated with vascular diseases.^{3,6} Among these risk factors, hypertension continues to be the most important for both AIS risk but also for hemorrhagic stroke risk. Among the nonmodifiable risk factors, increasing age and ethnicity, especially African American descent, are the most important.¹

Clinical Manifestations

A detailed discussion of the clinical manifestations of stroke is beyond the scope of this chapter, but a fundamental discussion is necessary to the understanding of stroke mechanisms and patient selection for percutaneous treatment, also known as EVT. This is especially important because, as discussed earlier, AIS and ICH or SAH can be complications of each other, and the major goal of EVT, whether in the acute setting or for stroke prevention, is the restoration of flow to the brain downstream of the stenosis or occlusion or the prevention of emboli and acute large vessel occlusion (LVO). Consequently, patency and prevention of ischemia within the territories of the perforating branches of the middle cerebral, basilar, and posterior cerebral arteries are generally not the direct goals of EVT. EVT purely for symptomatic perforator ischemia often results in completion of the stroke.⁷

Ischemic stroke is defined as a sudden (painless) loss of neurologic function. ICH and SAH, on the other hand, are typically associated with increasing headache (40%–50%) in the case of the former and a sudden severe headache in the case of the latter.^{8,9} Clinical manifestations of stroke are generally divided into anterior circulation (i.e., the internal carotid artery [ICA] territories) or posterior circulation (i.e., the vertebrobasilar [VB] territories). The clinical manifestations also vary depending on which side of the brain is affected. Although highly varied, some common syndromes can be easily identified and attributed to a particular arterial distribution. Their recognition is critical for the recognition of AIS and for acute LVO treatment. ICA territory strokes typically manifest with contralateral (to the occlusion) motor and sensory dysfunction generally affecting the face and arm more than the leg, and cognitive deficits, with or without loss of vision. Cognitive

deficits typically consist of aphasia in the case of dominant (usually left) hemisphere stroke and visual-spatial deficits and hemineglect in the case of nondominant (usually right) hemisphere stroke. Alteration of consciousness is uncommon in anterior circulation strokes, and if it occurs early in the clinical course, especially if associated with headache and nausea and vomiting, it suggests that an ICH or SAH are present.

Vertebrobasilar territory strokes are associated with crossed sensory-motor deficits often associated with severe dysarthria, disconjugate gaze or diplopia, ataxia, imbalance, and vertigo. Severe alterations of consciousness are more common than in anterior circulation strokes.

The majority of LVO strokes involve one or the other of the middle cerebral arteries (MCAs). The majority of the cerebral hemispheres are perfused by the MCA, which are therefore larger than the anterior cerebral arteries (ACAs) and are therefore the recipients of more emboli from the ICA. This is potentiated by the angulation of the ICA terminus, which generally gives off the ACA at an acute angle directing most flow into the MCA. The cervical ICAs carry roughly 80% of cerebral blood flow and are also the most common location for cerebral atherosclerosis.

A transient ischemic attack (TIA) can occur and herald a stroke.^{10,11} Although clinically defined as deficits lasting less than 24 hours, magnetic resonance imaging (MRI) often shows evidence of acute stroke in most events lasting just a few hours.¹² The type of symptoms experienced during a TIA can predict the risk of AIS within the coming days and weeks and is therefore a medical emergency.¹³

Diagnostic Evaluation

Because of the multiple mechanisms and clinical features of stroke, the diagnostic workup for patients with cerebrovascular disease is multifaceted. The first step is to distinguish between ischemic and hemorrhagic stroke, which is typically accomplished with a computed tomography (CT) scan of the brain. This is because CT is ubiquitous, has high sensitivity for ICH, and is rapid.^{8,14-17} Although MRI has greater sensitivity and specificity than CT for ischemia, it may be inadequate in detecting ICH in the ultra-early phases. The next step is to evaluate the cerebral vasculature in its entirety, that is, from the aortic arch to the intracranial vessels.^{18,19} Noninvasive angiographic techniques such as computed tomography angiography (CTA) are ideal for the same reasons as CT, although magnetic resonance angiography (MRA) is a reasonable alternative because it can be performed without the administration of contrast agents, but gadolinium-enhanced MRA of the arch is superior to MRA without gadolinium; these MRI techniques suffer from the same challenges as MRI, namely, lack of ready availability, sensitivity to motion, and relatively longer scanning and processing times. Artificial intelligence has revolutionized acute stroke evaluation with automated detection of LVO (usually limited to the MCA and its first-order branches), as well as the ability to rapidly analyze perfusion imaging. In the acute phase, the latter can detect regions of completed infarction (i.e. the infarct core) and differentiate them from regions of critically hypoperfused tissue that is still salvageable (i.e. the ischemic

penumbra). Revascularization therapy for AIS is geared toward rescue of the penumbra while minimizing infarct core growth and avoiding ICH.^{20,21}

Catheter-based cerebral angiography using digital subtraction (DSA) is still the gold standard for assessment of the cerebral arteries and veins but is typically performed electively when noninvasive means are discordant or non-diagnostic. Acutely, DSA is indicated in patients with LVO for the purpose of initiating revascularization therapy.

Laboratory studies evaluating coagulation and metabolic factors and various cardiac studies (electrocardiography, echocardiography) are also needed in most patients.^{13,14}

THE CEREBRAL VASCULATURE

The paired ICAs and vertebral arteries (VAs) supply blood flow to the brain in normal circumstances. Whereas the ICAs have no extracranial branches, the VAs give off feeders to the spine, spinal cord, and muscles of the neck. The ICAs travel cephalad and enter the skull through the carotid canal in the petrous bone. After the short horizontal and anteromedial course, they course through the cavernous sinus before they give off the first constant intracranial branch, the ophthalmic artery, which originates anteriorly just after the cavernous segment. The next (inconstant) branch of the ICA is the posterior communicating artery (PCoM), which serves as the major source of collateral flow between the anterior and posterior circulations. The anterior choroidal artery is the next branch before the ICA divides into the MCA and ACA ([Figure 25.1](#)). The MCA supplies flow to the basal ganglia by giving rise to the lenticulostriate perforating arteries from its dorsum. It then bifurcates (most common) as it enters the Sylvian fissure, giving off the superior and inferior, usually larger of the two, divisions, which then divide further to supply much of the frontal, parietal, and temporal lobes. The ACA courses medially to join the contralateral ACA in the midline, connecting with each other via the very short anterior communicating artery (ACom), and then supplying the inferior medial, anterior medial, and posterior medial portions of the ipsilateral frontal lobe.

The VAs arise from the subclavian arteries and course through the foramina transversaria of C6 to C1 before entering the foramen magnum. They each give off a posterior inferior cerebellar artery, the largest of the cerebellar arteries, and then join together at the vertebrobasilar junction to create the single basilar artery (BA). The latter, like the MCA, has numerous important perforators from its posterior wall supplying the pons and diencephalon. The anterior inferior cerebellar arteries arise on either side at the junction of the proximal and middle thirds of the BA. The superior cerebellar arteries, which are often duplicated, then arise from the basilar terminus just proximal to the origins of the bilateral posterior cerebral arteries, which supply the diencephalon and occipital lobes (see [Figure 25.1](#)). The posterior communicating artery (PCoM, inconstant) joins the ipsilateral PCA and ICA, which, along with the bilateral ACAs and ACom, form the circle of Willis. The

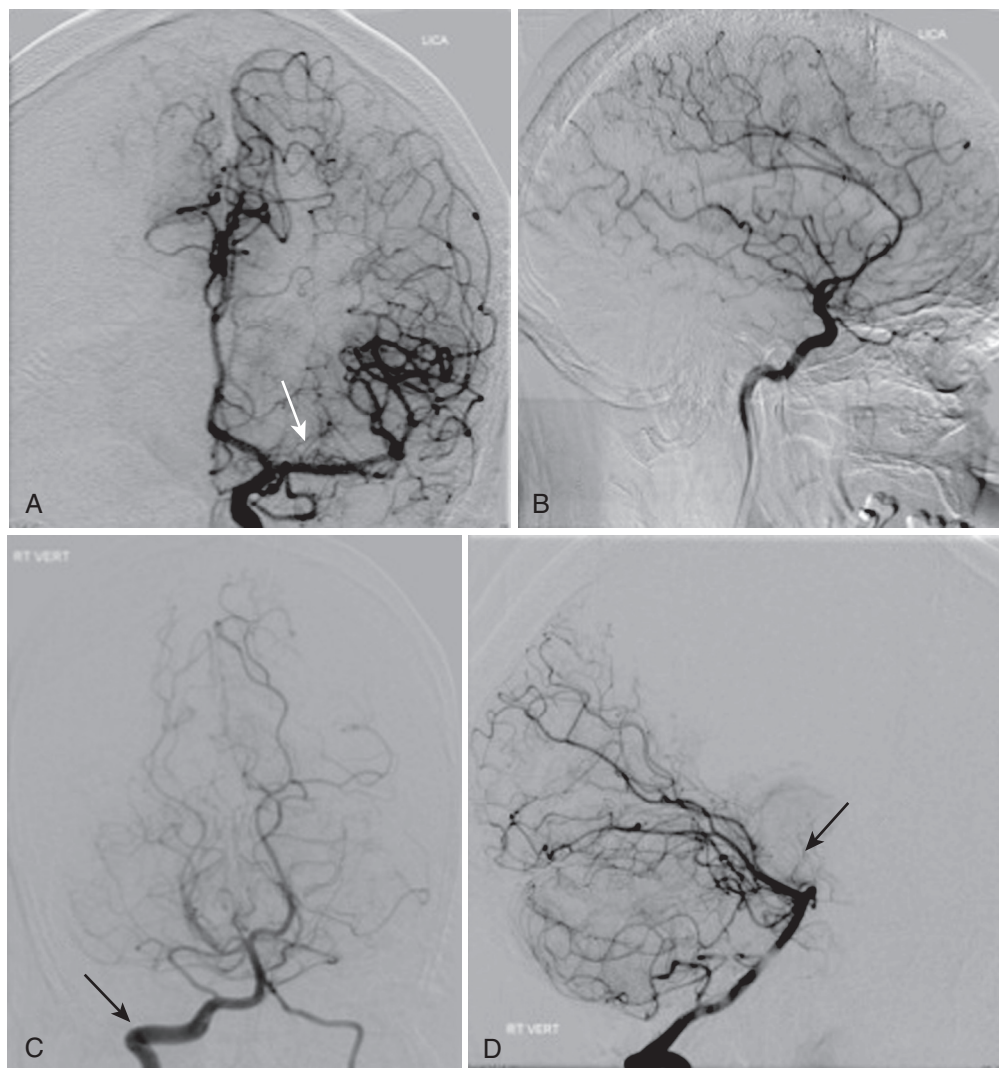


FIGURE 25.1 A selective left internal carotid angiogram shows normal intracranial branching pattern. The perforators (lenticulostriates) emanating from the middle cerebral artery trunk are easily identified (*arrow*) in the anteroposterior (AP) view (**A**). They are not visible in the lateral view (**B**), but the cortical branches of the middle cerebral and anterior cerebral arteries are well visualized. **C**, A right vertebral artery injection in the steep AP view shows the basilar artery and its branches well; note the dominant right vertebral artery (*arrow*). A lateral projection of a vertebral artery angiogram (**D**) shows the many small perforating branches emanating posteriorly from the basilar artery trunk as well as superiorly (*arrow*) from the basilar artery apex and posterior cerebral arteries.

complete circle is found in 25% to 40% of humans^{22,23} and is the major source of collateral flow at the base of the brain. There are many possible variations of the vessels of the circle of Willis, awareness of which is essential in understanding flow dynamics under pathological conditions.

The cerebral vasculature is histologically different from the somatic vasculature. The cervical muscular arteries become very thin and lose their adventitia and external elastic lamina within 1 cm of entering the skull base, making them more prone to injury and perforation during EVT compared with the coronary epicardial vessels for example. Most of the large cerebral arteries course on the surface of the brain within the subarachnoid space. Perforation or rupture of one of these arteries can result in SAH, ICH, or both, and because the brain is encased by the skull, this can cause a rapid and marked elevation of intracranial pressure,

which can then result in mass effect and cerebral herniation or a marked reduction of or cessation of cerebral blood flow. These are the most dreaded complications of all intracranial interventions, and their management is very challenging if not impossible without significant neurologic morbidity. Neurosurgical decompression of mass effect, hematoma evacuation, and treatment of hydrocephalus may be needed and may not be feasible with the concurrent use of antithrombotic, antiplatelet, and fibrinolytic agents typically administered during EVT.

The cervical and cerebral arteries can be very tortuous. Some segments of the vessels are encased in bony structures (e.g., the petrous ICA segment or are surrounded by or penetrate through the tough dura matter). All combined, the anatomic and histologic differences make the navigation of endovascular devices intracranially challenging and hazardous.

ACUTE ISCHEMIC STROKE TREATMENT

Indications and Contraindications

The first proven and approved AIS therapy was intravenous (IV) tissue plasminogen activator (tPA).²⁴ More than 2 decades later, only 10% of AIS patients in the United States are treated with IV tPA.²⁵⁻²⁷ This treatment is limited by a narrow time window of 4.5 hours²⁸; poor recanalization efficacy in LVO;^{29,30} especially for thrombi longer than 8 mm³¹; weak efficacy for patient with more severe strokes³²; no impact on stroke mortality rates³³⁻³⁶; and a posttreatment ICH rate of 3% to 6%.^{37,38} However, approximately one-third of patients will derive clinical benefit from tPA treatment with lower rates of disability at 3 months; therefore, all patients with AIS presenting within 4.5 hours from “last known well” and who do not have contraindications (i.e., any factor that increases systemic or ICH risk) should be treated with IV-tPA as quickly as possible.¹⁸

Endovascular therapy for the treatment of patients with AIS, which has literally transformed stroke care from a very risky and sometimes effective affair to one of the most effective therapies in all clinical medicine with safety comparable to medical therapy, became the standard of care in 2015 after the near-simultaneous publication of five randomized trials, leading to an immediate change in the American Heart/Stroke Associations (AHA/ASA) guidelines.¹⁸ These guidelines made the indications for EVT much clearer.¹⁸ Initially, the recommendation was for EVT to be offered to all patients within 6 hours of last known well who also had a proximal LVO (ICA or MCA) in the anterior circulation causing a stroke severity of 6 or more on the National Institutes of Health Stroke Scale (NIHSS) and who had radiographic evidence of a small infarct core and a significant penumbra. The presence of LVO is typically detected with CTA, although guidelines also allow for MRA.

In 2018, the AHA/ASA guidelines were again changed to recommend EVT treatment for a more selected group of patients within 24 hours of last known well and were then updated in 2019.³⁹ This was based on the publication of two randomized trials that tested EVT versus medical therapy.^{21,40} The relative benefit was even more robust than in patients treated earlier, principally because the prognosis for untreated LVO is so poor. These trials relied more heavily on perfusion imaging for patient selection. Consequently, the guidelines recommended advanced imaging such as perfusion imaging but did not prescribe the exact modality or criteria other than to recommend any of the criteria used in the randomized trials. This is because the utility of perfusion imaging remains controversial.⁴¹ There is some prospective evidence that MRI-based perfusion imaging is excellent at predicting response to EVT,⁴² but other data support CT perfusion, which was used, because of its speed and relative ubiquity, by many of the published trials showing efficacy of EVT.⁴³⁻⁴⁵ Others argue that these modalities only serve to restrict treatment because if they reveal a large infarct core of approximately 70 cc or more, then patients will be typically excluded from receiving EVT even if there is a much larger volume of tissue at risk. Furthermore, the specificity of these modalities for detecting the infarct core in the ultra-early window (i.e., the first few hours from stroke onset) is

unclear. These authors suggest that the so-called clinical-CT mismatch is a better selector of appropriateness for EVT.⁴¹ This approach uses the NIHSS and compares it with CT head evidence of early infarct signs as measured by the Alberta Stroke Program Early CT Score (ASPECTS); the latter is a 10-point scale with 10 representing a normal CT and 0 a complete infarct of the entire MCA territory.⁴⁶ If there is a disproportionately small volume of early hypodensity, then much of the brain is deemed to be viable, and EVT should proceed. This approach requires much greater skill in clinical and radiographic interpretation, but the use of perfusion imaging is now almost fool-proof thanks to the aforementioned artificial intelligence tools that rapidly determine infarct core and penumbra and present it in a color-coded manner to clinicians along with accurate measurements of the volume of tissue in each category.⁴⁷⁻⁵⁰ In general, however, a score of 7 or more on the ASPECTS scale is associated with good neurologic outcomes and roughly correlates with the 70-cc infarct core threshold.⁴⁶

The published guidelines do not make strong recommendations for treatment of posterior circulation LVO, primarily because most of the randomized controlled trials of EVT excluded those patients, and what little data are available show weak evidence for treatment.^{39,51,52} The contraindications for EVT are those that are associated with an increased risk of ICH or clinical futility. The larger the infarct core the greater the risk of ICH with either IV tPA or EVT.⁵³ A prior history of spontaneous ICH, any evidence of ICH or SAH on CT imaging, or an untreated previously ruptured aneurysm or arteriovenous malformation are also contraindications to IV tPA, although EVT can be considered in selected patients.^{18,39} A history of dementia, especially if moderate or severe, should be considered a contraindication because of the poor neuronal reserve, low probability of benefit, and much higher risk of ICH because of the presence of amyloid angiopathy in those with a history of Alzheimer's disease. EVT can be performed in patients receiving anticoagulants or antiplatelet agents, although there may be a higher risk of ICH if the patients have severe thrombocytopenia or hemophilia.⁵⁴ Increasing age is not a contraindication, and there is evidence that older patients derive relatively more benefit than younger patients, although fewer of them will survive.⁵⁵

Techniques

As with STEMI, improved outcomes with EVT are associated with shorter door-to-recanalization times, and as with STEMI treatment, this requires a coordinated effort by an experienced team of physicians, nurses, and technologists.^{56,57} In general, femoral access with an 8-Fr sheath should be obtained; longer sheaths should be used in patients with severe tortuosity. Radial access can be used but limits the size of the guide catheter to 6 or 7 Fr and is generally reserved for patients with posterior circulation LVO, especially if the aortic arch is steeply angulated. Then an 8-Fr balloon guide catheter is quickly advanced over an 0.035-inch wire into the aortic arch and used to cannulate the parent vessel. Aortic arch angiography and diagnostic angiography of the other vessels for

assessment of collaterals are strongly discouraged, and all necessary data should be gleaned from the CTA, which should always include the aortic arch. The interventionist should therefore be prepared in advance for any variations in aortic arch anatomy and choose the appropriate catheter shape in advance. It is the author's preference to use an 8-Fr balloon guide catheter that comes with a preshaped introducer inner catheter (8-Fr Flowgate, Stryker Neurovascular). This saves several minutes by avoiding the need to perform an over-the-wire exchange from the 5 or 6-Fr diagnostic catheter.

For ICA territory LVO, a CCA injection or roadmap can be performed in two planes of view, an ipsilateral oblique of approximately 30 degrees and a true lateral, and then a hydrophilic supportive guide wire should be advanced into the ICA if it is patent and followed by the guide catheter. If the ICA bulb is normal or has minimal disease on CTA and the occlusion is distal, then to save time, a skilled interventionist can advance the hydrophilic wire directly into the ICA without angiography or roadmapping using normal landmarks and known anatomic relationships (e.g., the ICA originates posteriorly and laterally compared with the external carotid artery [ECA]). If the ICA is occluded at the bulb, then the wire should be placed in the ECA and the guide catheter advanced into the distal CCA. If the LVO is in the VB system, then cannulation of the larger VA (typically the left) should be performed. In these cases, the 8-Fr balloon guide catheter can be placed in the subclavian artery, and an intermediate catheter will need to be used to cannulate the VA; alternatively, a long sheath (e.g., 6-Fr Slender Destination, Terumo Interventional Systems) can be placed in the VA if its size and tortuosity will allow.

Cannulation is followed by DSA with views of the entire contents of the calvarium in the cranial AP (Townes) and true lateral views. Image acquisition should include both arterial as well as the entire venous phases. Additional views are rarely needed. The goal is to identify the site of the occlusion, which may be obvious with an abrupt cutoff but may be more subtle and only identified by the presence of retrograde pial collaterals, the absence of a capillary phase in a wedge shape, or early venous shunting; the latter is typically associated with completed infarction. The presence of and sources of collateral blood flow should be identified, typically pial collaterals from the ACA branches, the presence of which is correlated with improved outcomes and a decreased ICH risk.⁵⁸⁻⁶⁰ Particular attention should be paid to the presence of normal variants that may complicate therapy such as persistent fetal anterior-to-posterior circulation branches (e.g., persistent trigeminal artery), the inadvertent occlusion of which can be catastrophic. Hazards such as large thrombosed aneurysms, arteriovenous malformations (AVMs), or findings suggestive of chronic occlusions should be identified to guide the decision on the best approach or the decision to not treat.

Heparin is no longer routinely given because it was associated with increased rates of ICH in a randomized trial of intraarterial thrombolysis (IAT). However, continuous flush with heparinized saline is required in all catheters. Heparin can be given judiciously if stenting is required.

After identification of the site of the occlusion and with stable access obtained, an 0.014-inch hydrophilic, soft-tipped wire (e.g., Synchron, Stryker Neurovascular) should be advanced along with a microcatheter (e.g., Rebar, Medtronic). The wire is used to carefully cross the occluded segment, which requires knowledge of the expected course of the occluded vessel and its branch points and is greatly facilitated by biplane imaging and high-quality roadmapping. Sometimes the pial collateral flow is so robust the occluded vessel fills retrograde up to or near the distal face of the thrombus, which makes wiring much safer. The wire tip must avoid cannulation of the smaller branches and perforators arising from the ICA (PCoM, anterior choroidal), the MCA (lenticulostriates), the VA (posterior inferior cerebellar, anterior spinal), the BA (anterior inferior and superior cerebellars, pontine and diencephalic perforators), and posterior cerebral arteries (thalamoperforators, thalamogeniculates, and others). Cannulation of these smaller branches can lead to devastating ICH. The microcatheter can then be advanced beyond the occlusion and the wire removed. Some advocate for microcatheter injection, although there is some evidence that these injections can increase the risk of ICH.⁶¹ The author's approach is to gently aspirate with a 1-cc syringe and look for free flow of blood to confirm an intraluminal location of the catheter tip.

Intraarterial Thrombolysis

Several thrombolytic agents have been used for IAT, including streptokinase, t-PA, and rpro-UK.⁶²⁻⁷² The only agent for which there is robust clinical support is rpro-UK, which was used in the Prolyse in Acute Cerebral Thromboembolism (PROACT) I and II trials.^{72,73} These trials enrolled patients with MCA occlusion within 6 hours of last known well and required a 2-hour infusion of the drug within the clot in the treatment arm. Although the PROACT II trial was the first positive trial of EVT for stroke, the agent, rpro-UK, is not commercially available, and the Interventional Management of Stroke (IMS) III randomized controlled trial (RCT) of adjunct intraarterial (IA) tPA was futile,⁷⁴ although some recent data suggest there may be benefit in the addition of IA tPA to MT.⁷⁵ With the advent of mechanical thrombectomy (MT), the use of IAT is no longer recommended (AHA guidelines). This approach can be considered in rare circumstances of an occlusion of a small and critical branch that cannot be accessed with MT. The major limitation of IAT is that it is relatively slow in achieving recanalization and increases the risk of ICH.⁷⁶ If this approach is used, the guiding principle should be to use the lowest dose possible of the safest thrombolytic possible (e.g., tenecteplase, for which there is an increasing body of safety and efficacy data).⁷⁷⁻⁸⁰ Younger patients with small infarct cores and no hypertension, normoglycemia, and short durations of ischemia may be ideal candidates for this technique.

Combining thrombolytics and glycoprotein (GP) IIb/IIIa antagonists has been described, and ongoing clinical trials are testing the addition of these agents to MT.^{70,81,82} In the absence of robust data showing safety and efficacy, it is the author's approach to use GP IIb/IIIa antagonists when there is an atherosclerotic occlusion and a residual severe stenosis after MT or when emergency stent implantation is needed. Continuous infusions have been associated with

high ICH rates; therefore, the lowest dose of the shortest acting agent possible should be given.⁸³ The author's approach is to administer them intraarterially at about one-quarter to half of the usual coronary loading dose immediately before stent placement.⁸¹

Combined Intravenous-Intraarterial Thrombolysis

The IMS III trial was an RCT that enrolled 656 of a planned 900 patients presenting within 3 hours of last known well. The patients were treated with IV tPA alone or IV tPA plus EVT,⁷⁴ which consisted mostly of IA tPA (80%) but also included the available MT devices such as the MERCI Retriever (Stryker Neurovascular; 28%), the Penumbra aspiration system (Penumbra Inc.; 16%), EKOS (Boston Scientific; 6.6%), and Solitaire (Medtronic; 1.5%). Unfortunately, the study was terminated early because of futility, although there were no safety concerns. Much was learned from the trial, including the importance of patient selection using CTA and the rapid initiation of EVT and that combined IV and IA thrombolysis without MT is no better than IV thrombolysis alone.^{74,84,85}

With the advent of MT as the standard-of-care LVO treatment, questions have been raised regarding the continued utility of IV tPA when an accessible LVO is present, as well as the safety of combining IV tPA with MT. Although a major prospective RCT has yet to answer this question, there is mounting evidence that following IV tPA with MT is very safe, and there is no need to delay MT to see if patients respond to IV tPA. The AHA/ASA guidelines clearly support administering tPA and then proceeding directly to the neurointerventional suite for MT.^{18,86} Furthermore, several studies have shown that there may be added benefit in combining the two therapies rather than skipping IV tPA in favor of MT.⁸⁷ The reasons for this include the fact that small distal occlusions are inaccessible by MT, and thrombosis of the small arterioles and capillaries downstream of the proximal LVO may all respond to the thrombolysis. Furthermore, delays in MT initiation can occur, especially in patients who need to be transferred to a larger center for MT, and having thrombolytics on board may increase the chances of recanalization and offers the patient some treatment in case MT cannot be performed because of logistics or difficulty in accessing the site of the LVO. Therefore, the current standard of care is that IV tPA should never be withheld or delayed in favor of MT.³⁹

Mechanical Embolectomy

Mechanical clot removal or MT was first described in the late 1990s with operators reporting using snares designed for foreign body removal to extract clots from the brain.^{88,89} The first Food and Drug Administration (FDA)-approved device designed for MT in the brain was the Merci retriever, which was designed to be used in conjunction with a balloon occlusion guide catheter. This device revolutionized the approach to LVO when approved in 2005 but without an RCT showing clinical benefit, adoption was slow, and many vascular neurologists were skeptical of referring patients for an unproven therapy. The second device approved for thrombectomy was the Penumbra Aspiration System. This consisted of a vacuum pump, three catheters varying between 3- and 5-Fr diameters and a Separator wire, which was a microwire with a silastic bead on its tip

that would be used to break up the clots in the tip of the catheter to facilitate aspiration. However, similar to the Merci device, because of the lack of an RCT showing clinical efficacy, the use of the device was limited. It was not until the advent of stent retriever technology that the care of patients with AIS changed fundamentally.

The stent retrievers first received FDA approval in 2012, and it quickly became clear that they were game changers in terms of recanalization efficacy as well as safety. By the time the first RCT was completed, two devices were in use in the United States: the Trevo retriever (Stryker Neurovascular) and the Solitaire FR (Medtronic). These devices consist of nitinol self-expanding stents that are welded to an 0.014-inch wire on one end and could be delivered through a 2.3-Fr microcatheter. After the device is deployed within the thrombus, it typically creates an immediate channel for antegrade flow. Within a few minutes, the device is retracted into a balloon guide catheter (BGC) with the balloon inflated to block antegrade flow and with aspiration on the guide catheter central lumen to create retrograde flow to facilitate the thrombectomy. This remains the fundamental technique for MT; proximal flow arrest and aspiration with a BGC is critical and has been shown to greatly improve recanalization efficacy and neurologic outcomes.⁹⁰

As described earlier, the BGC is advanced into the cervical ICA, the more distal the better but paying attention to ICA tortuosity, which can increase the risk of dissection by the BGC. When the microcatheter has passed beyond the site of occlusion, the stent retriever is advanced and deployed slowly with most of the device deployed distal to the distal face of the clot and the ideally the proximal retriever deployed at the proximal face of the clot. Longer retrievers (4–5 cm) appear to be more effective than shorter ones (2–3 cm), and similarly, larger diameter retrievers (5–6 mm) tend to be more effective than 3- to 4-mm devices, although in the author's experience, the very small devices appear to work well in very small second- and third-order branches that measure 1.5 to 2 mm in diameter. It is best to leave the retriever deployed for anywhere between 3 and 5 minutes (the author prefers 4 minutes) to allow the nitinol to expand fully and to integrate the thrombus within the stent tines (Figure 25.2 and eFigure 25.3). The balloon on the guide catheter is then inflated to block all antegrade flow, and then using either a 60-cc syringe and an assistant or a mechanical vacuum pump to create retrograde flow, the retriever is slowly withdrawn along with the microcatheter into the guide catheter. Timing is critical because rapid withdrawal can cause loss of friction between the retriever and the thrombus and can result in loss of the thrombus or fragmentation and reocclusion or embolization to a new territory. This is especially important as the device enters the relatively acute angle at the ICA terminus and the cavernous segment. After the device has been completely removed and the balloon guide has been completely cleared of any potential thrombi, the balloon can be deflated, and control angiography can then be performed. The devices are typically labeled for a total of three passes before they must be exchanged, but because they are made of nitinol, they are very robust. However, with an increasing number of passes, there is greater risk of complications (spasm, vessel injury, dissection, and

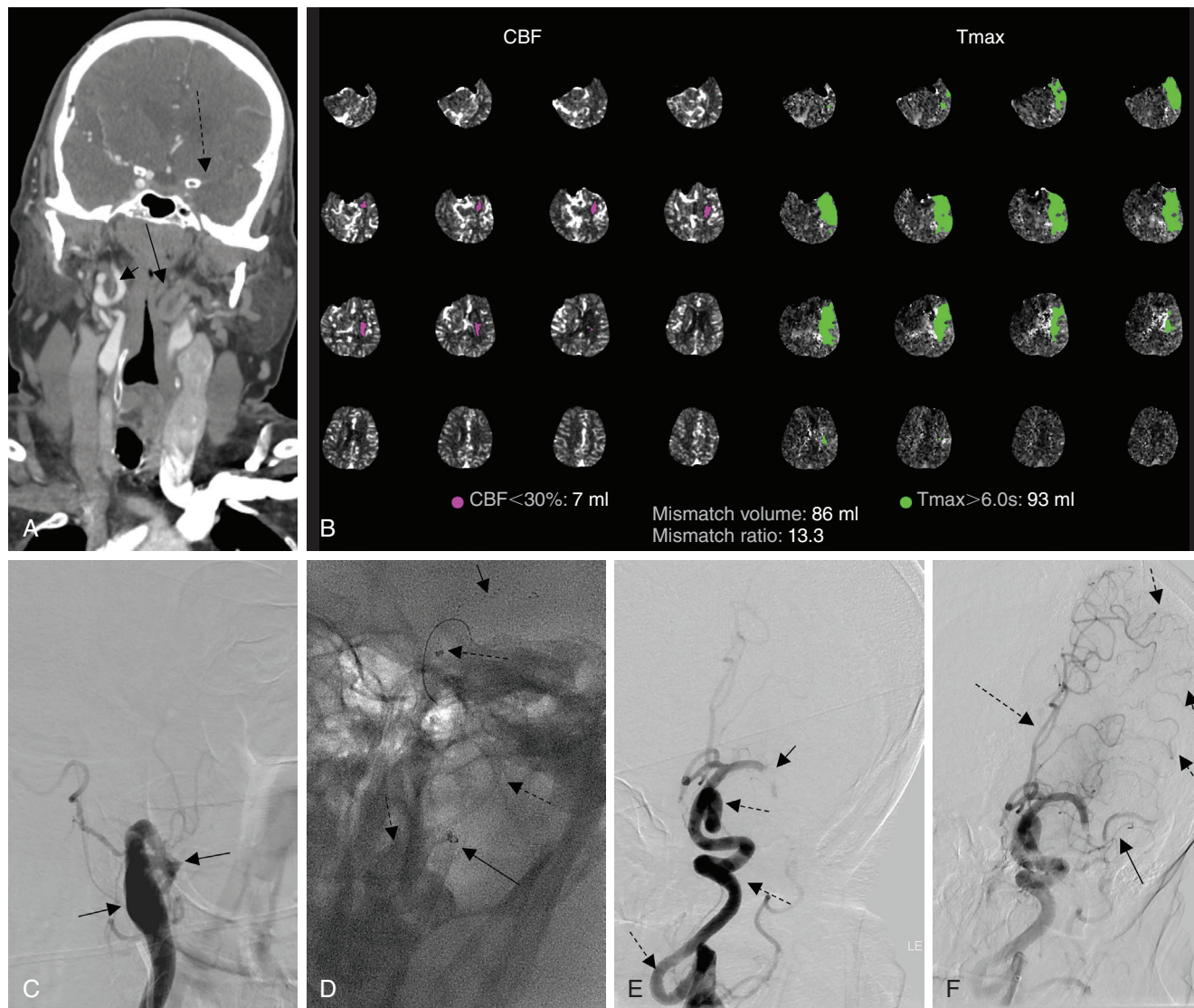
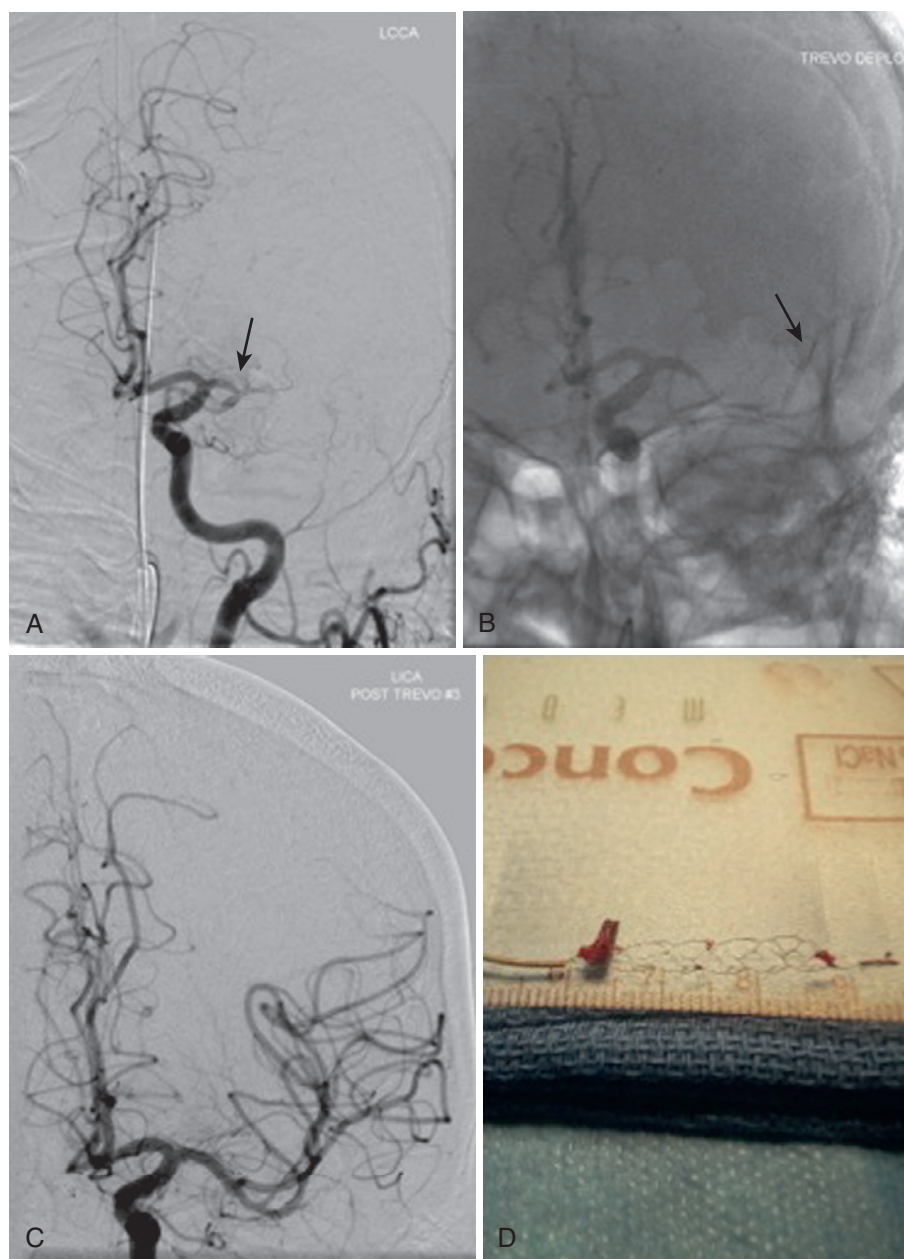


FIGURE 25.2 A 75-year-old woman with a history of atrial fibrillation and COVID-19 infection presented with a left middle cerebral artery syndrome. The National Institutes of Health Stroke Scale (NIHSS) score was 20, and computed tomography angiography (**A**) showed occlusion of the left internal carotid artery (ICA) (*long arrow*), which was very tortuous similar to the right ICA (*short arrow*). The left middle cerebral artery (MCA) was also occluded (*dashed arrow*). The computed tomography perfusion scan was processed with an artificial intelligence platform, which revealed the presence of a small infarct core of 7 cc (cerebral blood flow <30%, *pink region*) and a large penumbra of 86 cc (Tmax >6 seconds, *green region*), justifying intervention. Angiography (**C**) confirmed the ICA occlusion and tortuosity (*arrows*), but the bulb was patent, suggesting that this was a carotid terminus occlusion. The first intervention (**D**) was performed by placing an 8-Fr balloon guide catheter (*long arrow*) in the ICA bulb because of the tortuosity, which can be visualized by the complex course of the 6-Fr aspiration catheter (*short dashed arrows*) whose tip could not be advanced beyond the ICA terminus (*long dashed arrow*). A 6- × 40-mm stent retriever was deployed in the MCA trunk extending into the ICA terminus (*short arrow*). After withdrawal of both devices under balloon guide suction (**E**) a large thrombus was removed, and the ICA was recanalized, although the MCA had a persistent distal occlusion (*arrow*). Note the extreme tortuosity with three separate areas of redundant loops and S turns (*dashed arrows*), which greatly prolonged the procedure and resulted in frequent prolapse of the guide catheter out of the ICA. After three more passes with the stent retriever (**F**), two of which were performed with the aid of a 5-Fr distal aspiration catheter, which was successfully advanced into the distal left MCA, there was TICI2a recanalization of the MCA with only partial antegrade flow (*arrow*), although there were robust pial collaterals (*short dashed arrows*) from the anterior cerebral artery (*long dashed arrow*) to the MCA territory. The patient began to speak a few words and could move the right arm slightly, resulting in termination of the procedure 2 hours after starting. By the next morning, the NIHSS score had improved to 6.

endothelial denudation) and decreased probability of good outcomes.⁹¹⁻⁹³ In fact, the goal of MT should be to achieve revascularization with the first pass, which is one of the best predictors of good neurologic outcomes.⁹⁴

Shortly after widespread use of the stent retrievers, reports emerged of variations on the thrombectomy technique. These included combining stent retrievers with distal aspiration catheters that can be navigated into the

ICA terminus or MCA trunk either with or without proximal flow arrest. The stent retriever is then deployed distally, and during retrieval, the retriever is partially or wholly withdrawn into the aspiration catheter; then they are either withdrawn out of the body together under aspiration or, as discussed later, the stent retriever can be withdrawn through the distal aspiration catheter, which is kept in place and ready for another pass if needed. Some



eFIGURE 25.3 A left common carotid artery injection in the anteroposterior view (**A**) shows a complete left middle cerebral artery occlusion (*arrow*) in a patient who failed to recanalize with intravenous tissue plasminogen activator. A Trevo stent-retriever device was deployed in the middle cerebral artery with half deployed distally in a secondary branch (*arrow* in **B** points to the device tip). After the third pass with the device, there was complete recanalization of the middle cerebral artery (**C**), and the thrombus was ensnared in the device (**D**).

have dropped the stent retrievers altogether and began performing aspiration with these newer distal aspiration catheters with reports of quicker and better recanalization. These techniques have many names and many proponents, but none has been as studied prospectively as the combination of a stent retriever and a BGC, and none has been proven to be superior; therefore, the combination of a stent retriever with a BGC should be the first-line technique as supported by the AHA/ASA guidelines.^{18,95,96} However, there are circumstances when a primary aspiration technique or distal aspiration combined with a stent retriever may be the ideal approach. In cases with severe proximal stenoses or dissection or in patients who require a proximal ICA stent to permit access to the distal LVO, placement of a distal aspiration catheter can prevent the need to reobtain access through a disease segment and most important will prevent a stent retriever from being dragged through a stenosis or dissection, thus avoiding more injury and avoiding snaring of the proximal stent with the retriever, which can be difficult or impossible to disentangle. Also, for patients with VB occlusions in whom the 8-Fr BGC is too large to place in the VA and therefore in whom true retrograde flow cannot be established, placement of a distal aspiration catheter can facilitate the thrombectomy; there is some evidence to suggest this approach may be superior in BA occlusion.⁹⁷

There is a seemingly innumerable number of distal aspiration catheters from multiple manufacturers on the market. Most of them are similar in sizes with internal diameters of 035, 045, 055, 060, 071, and even 088 inches. Some are more deliverable than others and can reach second- and third-order MCA branches. Their use requires some skill in navigation and often requires a large and supportive base catheter or sheath and a microcatheter or inner catheter. Also, some of the devices are so flexible that their inner linings can be damaged by the stent retriever if it is withdrawn within them. The operator must also make sure to choose a device of adequate length to reach the desired segment, especially in cases in which the base catheter or sheath cannot be placed distally enough in the parent vessel. The author recommends becoming familiar with only one or two such catheters and their sheath and guide requirements to decrease the guesswork work during an LVO intervention.

Balloon Angioplasty and Stenting

Although in the United States the majority of LVO are caused by embolic occlusion, mostly from a cardioembolic source, acute occlusions caused by an underlying atherosclerotic plaque also occur, especially in patients with cervical ICA (i.e., carotid bulb) stenosis. In certain populations, atherosclerotic disease of the intracranial vessels can also be a cause of LVO. This is especially true in patients who are of Southeast Asian descent. In China, for example, the most common cause of stroke is intracranial atherosclerotic disease. The author has long argued that the EVT approach should be tailored to the underlying pathophysiology, but this is controversial and not reflected in the available RCT or US guidelines.^{18,81} Large series from Japan have reported recanalization rates of

91% with balloon angioplasty alone with lower ICH risks than IA fibrinolysis (3% vs >10%).^{98,99} Although these results cannot be generalized because of the much lower incidence of intracranial atherosclerotic disease (ICAD) in the United States, they provide tantalizing support for the judicious use of angioplasty and stenting in patients with suspected ICAD.^{81,100-104} Differentiating embolic occlusion from atherosclerotic occlusion can be challenging, and anecdotal reports and experience with stent retriever use in patients with ICAD has shown remarkable efficacy. One approach therefore is to use a stent retriever for all, and then if an underlying stenosis is found, a decision can be made on the appropriateness of angioplasty and stenting. The former requires the use of an undersized balloon because of the risk of vessel rupture, and the latter requires potent antiplatelet therapy during and after the procedure, which can theoretically increase the risk of ICH in some patients as described earlier. This approach is unproven and will require off-label use of commercially available devices (see later section called Intracranial Angioplasty and Stenting).

In cases of tandem occlusion (i.e., atherosclerotic cervical ICA occlusion at the bulb with distal ICA terminus occlusion or MCA occlusion), angioplasty and stenting may be necessary to permit access to the distal LVO.¹⁰⁴⁻¹⁰⁹ Preliminary experience with this approach shows that it is generally safe and effective. A challenge of this approach is sometimes navigating through a severe, calcified underlying stenosis without being able to visualize the lumen. The major challenge, however, is the timing of the ICA stenting. Acute stenting generally requires GP IIb/IIIa antagonists, and in patients with known large infarct cores or other high-risk factors for ICH, stent placement may not be appropriate. In these patients, balloon angioplasty alone may be appropriate in the hopes of maintaining patency long enough to allow the patient to recover and then more definitive treatment in 2 to 4 weeks when the risk of ICH will be lower.

The other challenge is whether to revascularize the proximal occlusion first or the distal tandem occlusion. The argument supporting treating the distal occlusion first is that if the MCA can be recanalized, then despite the ICA occlusion, collateral flow via the ACom or PCom may be sufficient to maintain brain viability in case the cervical ICA segment cannot be kept open or the intervention takes longer than expected. Also, the absence of a stent in the proximal ICA keeps therapeutic device options open because of the lack of risk of stent and stent-retriever entanglement. The drawbacks of treating the distal occlusion first are that it may not be feasible if the proximal lesion is very calcified and does not permit passage of a BGC or large-bore aspiration catheter. Second, if the distal vessel is recanalized, there is always a chance of reocclusion from emboli arising during the proximal intervention, although some anecdotal and retrospective data suggest the opposite.¹¹⁰ Third, proximal recanalization greatly increases in-flow and can sometimes result in spontaneous recanalization of the distal LVO.

Finally, EVT for acute cervicocranial dissection-associated LVO remains untested. In general, these patients should be

treated much the same as other patients with LVO, but the major challenge is traversing the dissection, especially because patients with spontaneous cervicocranial dissections are very likely to have extreme tortuosity and redundant loops in the ICA and VA.¹¹¹ Stenting is often required if the dissection is flow limiting or occlusive, either before or after treatment of the tandem occlusion, if any; however, this is very challenging because the available self-expanding stent systems are typically too rigid to be deliverable through the tight turns and loops often associated with dissection.¹¹²⁻¹¹⁵ Newer devices designed for the treatment of wide-necked cerebral aneurysms may be needed.¹¹⁶

Clinical Outcomes

Before February 2015, the data on outcomes for EVT were highly varied with major differences in patient selection, LVO location, LVO cause, endovascular techniques, and periprocedural antithrombotics and anticoagulants, leading some to conclude that there was no net benefit from EVT.⁶⁸ The PROACT II trial has already been mentioned, and now it seems pointless to discuss other trials of IAT alone other than to say that some fibrinolytics may be effective in selected patients as discussed earlier.^{72,117} The Merci Retriever and Penumbra Aspiration and Separator wires are no longer manufactured and have been supplanted by the stent retrievers, the efficacy and safety of which have been proven at an unprecedented level.

After the failure of the IMS III trial to show benefit of EVT, there was a concerted rethinking of the future of EVT for AIS treatment. The preliminary experience with the stent retrievers was very promising, but only RCTs would convince the vascular neurology community that EVT was a viable treatment option. Hence, several trials were initiated around the same time. The trial designs had many similarities in that EVT would be tested against best medical therapy, and the focus would be on anterior circulation strokes with confirmed LVO and, importantly, with documented tissue at risk with small infarct cores. Five trials were initiated in the United States, Canada, and Europe using one of the two stent retrievers on the market at the time (Solitaire or Trevo). The first hint that there would be clinical benefit was with the presentation of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial data at the European Stroke Organization meeting in October 2014. This trial used a pragmatic design and did not use advanced imaging to select patients (it was designed in 2010 before the publication of IMS III), and it was conducted only in the Netherlands; therefore, it was unlike the other four ongoing trials.¹¹⁸ The trial enrolled 500 patients with AIS within 6 hours of stroke onset, the majority of whom were treated with IV tPA (89%). Patients were randomized to medical therapy with or without EVT, primarily EVT with a stent retriever (81.5%). The outcome was an adjusted common odds ratio for good neurologic outcome at 3 months, which was 1.67 (95% confidence interval [CI], 1.21–2.3) in favor of the EVT arm. The absolute difference in good outcomes was 13.5%

(32.6% vs 19.1%) with no difference in mortality rate or the risk of symptomatic ICH. Based on these results, there was an immediate evaluation of the safety data in the ongoing trials because of the ethical concerns of randomizing in the presence of new data showing benefit. Remarkably, all four of the other trials were stopped early, and all four showed overwhelming clinical efficacy. All the trials were presented back to back at the International Stroke Conference on February 11, 2015.^{45,119-121}

Of these four trials, the ESCAPE trial was the most important because it was the furthest along when it was stopped.¹¹⁹ In this international study, 316 patients were randomized within 12 hours of stroke onset to best medical therapy with or without MT (stent retrievers and BGC were recommended). The randomized patients had to have a CTA-documented LVO, an ASPECTS score of 6 to 10, and good collaterals by multiphase CTA; the latter is another method of assessing perfusion and is less sensitive to motion artifact. Most of the patients were treated with IV tPA (75.3%), and EVT had to be initiated quickly after randomization. The study set targets for groin puncture within 60 minutes of CT scan completion and first reperfusion within 90 minutes. Using these rigorous methods paid off because the primary outcome of functional independence at 90 days was 53% in the treatment arm and 29.3% in the control group ($P < .001$). The common odds ratio was 2.6 (95% CI, 1.7–3.8; $P < .001$). The reperfusion rate was 72.4% using the Thrombolysis in Cerebral Infarction (TICI) grading score, which was loosely based on the coronary reperfusion scoring system.¹²² Importantly, this was the first stroke trial to show a reduction in mortality rate—10.4% versus 19% ($P = .04$). Just as remarkable was the symptomatic ICH rate of 3.6% compared with 2.7% in the control group ($P = .75$). The number needed to treat was 4.2. The other three trials presented that day had equally compelling outcomes: Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) ($n = 196$) had an unadjusted relative risk of 1.7 (95% CI, 1.23–2.33), Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT) ($n = 74$) had an effect variable odds ratio (OR) of 2.0 (95% CI, 1.1–3.5), and Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND-IA) ($n = 70$) had an effect size of 3.8 (95% CI, 1.4–10).^{45,120,121} The significance of that day cannot be overstated. After the publication of the IMS III trial in 2013, there was general despondency among the neurointerventional community, and there were serious discussions of terminating all fellowship training, so one can only imagine the significance of five randomized trials being positive. Literally overnight, the field of neurointerventional went from being a somewhat niche specialty focused on the treatment of patients with aneurysms and cerebral AVMs to one that offers an incredibly effective treatment for one of the most important diseases in the world. Consequently, the AHA/ASA guidelines were changed to reflect the new evidence but with a 6-hour window because most of the patients enrolled in these trials were treated within 6 hours.

Real-world experience with MT and large meta-analyses have confirmed the efficacy of MT in the population at large as well as in many subgroups.^{55,96,123,124}

Because many stroke patients present beyond 6 hours, this meant that many patients would not receive treatment per guidelines. The author and others had previously published several series of patients treated well beyond the traditional time window of 6 hours with similar outcomes to those treated under 6 hours both in the anterior and posterior circulations.^{125,126} This led to the design and completion of two RCTs comparing MT versus medical therapy in patients up to 16 hours from last known well²¹ and 24 hours from last known well.⁴⁰ These trials differed slightly in the patient selection criteria, in particular the perfusion inclusion criteria: DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) trial used a tiered selection system based on the age and size of the infarct core with patients older than 80 years of age required to have an infarct core smaller than 21 cc, and those younger than 80 years, the infarct core had to be smaller than 31 cc, but those with a NIHSS score of 20 or greater were allowed to have an infarct core 31 to 50 cc.⁴⁰ The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE) 3 trial required an infarct core smaller than 70 cc with a mismatch volume of 1.8 or greater and a minimum mismatch volume of 15 cc.²¹ Importantly, the trials used a commercially available artificial intelligence platform (RAPID, Ischemia View Inc) to process the perfusion data. Both trials easily achieved their main endpoints. In DEFUSE 3, the OR for good functional outcome at 90 days was 2.77 (95% CI, 1.63–4.7; $P < .001$), and the mortality rate was 13% versus 23% ($P = .05$) with no difference in symptomatic ICH (6% vs 4%; $P = .75$). In DAWN, the absolute difference for good functional outcome at 90 days was 35.5% (49% vs 13%; posterior probability of superiority $>0.999\%$) with no differences in symptomatic ICH (6% vs 3%; $P = .5$) or mortality rate (20% vs 18%; $P = 1$). The number needed to treat in DAWN was two. The AHA/ASA guidelines were changed on the same day that the trials were presented in January 2018 and expanded the time window to 16 and 24 hours depending on the perfusion criteria used.¹²⁷

Based on these results and the author's prior experience, it is reasonable to assume that the duration of ischemia is no longer relevant as the sole criterion for selecting patients; more important are the volume of the infarct core and the size of the ischemic penumbra regardless of stroke duration, but this approach is beyond the published guidelines. In addition to this issue, there are many unanswered issues with MT treatment for LVO: should posterior circulation occlusion be treated? Should occlusions of smaller branches (ACA, second- and third-order MCA branches) be treated? Should patients with LVO but minor deficits be treated with MT? How large of an infarct core is too large for treatment, and if so, how should it be measured? Should perfusion imaging be used in the ultra-early patients, those under 6 hours, only in those in the 6- to 24-hour window, or not at all? Is there any role for angioplasty and stenting? Should distal aspiration be used? If so, when and with which devices? Should adjuvant

thrombolysis or GP IIb/IIIa antagonists be used routinely? Should patients with pediatric stroke be treated with MT? What about periprocedural management? Should blood pressure be lowered if elevated? If so, when—before, during, or after revascularization? If lowering is appropriate, to what level and for how long? What about anesthesia for the procedure? General, conscious sedation, or local anesthesia only? This latter question has been very controversial since the author and colleagues published multiple large series that showed significantly worse neurologic outcomes and higher mortality rate in patients treated under general anesthesia.¹²⁸⁻¹³¹ Analyses of the large RCT of MT and multiple large registries and meta-analyses have also supported these findings.¹³²⁻¹³⁵ Three very small, single-center RCTs were performed that showed no difference in outcomes or marginal benefit of general anesthesia.¹³⁶⁻¹³⁸ Randomized trials are ongoing to address this issue, but given the increased costs of general anesthesia and lack of clear benefit, the AHA/ASA guidelines support the use of conscious sedation.¹⁸ What is not controversial is the fact that patients should be managed postoperatively in dedicated stroke or neurologic intensive care units by nurses and physicians experienced in stroke care.¹⁵

Intracranial Angioplasty and Stenting

Intracranial atherosclerosis is responsible for 8% to 10% of ischemic strokes in the United States.^{1,139-141} Because of the difficulties in direct visualization of the intracranial vessels, other conditions have to be considered whenever an intracranial arterial stenosis is detected, including vasculitis (autoimmune and infectious), spontaneous dissection, partially recanalized embolism, reversible cerebral vasoconstriction syndrome, moyamoya arteriopathy, and post-radiation arteriopathy.¹⁴²

Intracranial atherosclerotic disease generally occurs in the proximal intracranial vessels—the cavernous and supraclinoid ICAs, the MCA trunk, the distal VA, the proximal and middle thirds of the BA, and the proximal PCAs. Although ICAD can involve second- and third-order branches, these vessels are generally too small to be treated with angioplasty and stenting, and they should be avoided; if there is primary involvement of these distal branches and the patient does not have diabetes, then central nervous system vasculitis should be considered, especially if there are headaches and strokes in multiple territories. The ACAs can also be involved, but their acute take-off from the ICA terminus makes device navigation particularly difficult, and they tend to be smaller than 2 mm proximally, further making EVT challenging.

In the WASID (Warfarin-Aspirin for Symptomatic Intracranial Disease) RCT, an unusual medical regimen was compared (warfarin vs aspirin 1300 mg); unsurprisingly, the rate of recurrent stroke was approximately 22% per year in both groups.^{140,143} Surgical bypass procedures have been ineffective, and endarterectomy is very challenging.¹⁴⁴ With advances in coronary balloons and stents, EVT was used to treat patients with ICAD beginning in the mid to late 1990s. In the 2000s, several devices were designed and tested specifically for the treatment of patients with ICAD. This led to the SAMMPRIS (Stenting and Aggressive

Medical Management for Preventing Recurrent Stroke in Intracranial Arterial Stenosis) RCT of a self-expanding stent designed for the neurovasculature (Wingspan, Stryker Inc.) plus maximal medical therapy (MMT) versus MMT alone. In this study, MMT consisted of dual antiplatelet therapy (DAPT) plus aggressive risk factor modification. Not surprisingly, the medical therapy performed much better than expected, and the EVT arm had worse outcomes.¹⁴⁵ This trial has effectively eliminated support for EVT for ICAD, although the trial had several weaknesses that in the opinion of the author greatly limit its generalizability (to be discussed later).¹⁴⁶

Indications and Patient Selection

Endovascular therapy is generally indicated for patients who have symptomatic ICAD that has failed MMT. Furthermore, treatment should be restricted to patients who have an angiographically proven 70% or greater stenosis because in the Warfarin-Aspirin for Symptomatic Intracranial Disease (WASID) trial, stroke recurrence risk for greater than 50% intracranial stenoses was approximately 12% per year but nearly 22% in those with a greater than 70% stenosis; however, in SAMMPRIS, it was 12.2%.^{143,145} Therefore, to justify EVT, which carries substantial risks, the risk of stroke must be very high with MMT alone. For these reasons, the author limits EVT to patients who not only meet these above criteria but who also have impaired cerebrovascular reserve (i.e., have hemodynamically flow-limiting stenoses with poor collaterals).¹⁴⁶⁻¹⁴⁹ Cerebrovascular reserve can be measured noninvasively with transcranial Doppler ultrasonography, single-photon emission computed tomography, computed tomography perfusion (CTP), or positron emission tomography scanning; the latter is the gold standard but is not as readily available as the other modalities. For all these studies, a vasodilatory stimulus must be administered, and the normal cerebral blood flow augmentation can then be measured; this is typically achieved with the administration of acetazolamide, but even breath-holding can achieve the same effect. Another method of determining the presence of impaired cerebrovascular reserve is the presence of hemodynamic TIAs, that is, focal symptoms that occur with lowering of blood pressure into normal or slightly elevated ranges or that occur upon standing; the latter are very suggestive of critically impaired cerebral blood flow.

It is also essential that the patient's symptoms should be attributable to ischemia in the territory distal to the stenosis and not caused by ischemia in a perforator arising from the stenosis.¹⁴⁶ As discussed earlier, patients who present with ischemia of perforators would not be expected to derive benefit from angioplasty and stenting because of the probability of "snowplowing" of the plaque and occlusion of the perforator. There is also emerging evidence that EVT should be delayed for 7 days since the last stroke because of the higher risk of stroke and ICH in those treated earlier.^{145,150,151} Some have even advocated for a longer delay of more than 6 weeks.¹⁵²

Angiographic characteristics are also important: lesion length, vessel diameter and stepoff in size between branch and parent vessel, eccentricity, calcification, angulation,

extension into a bifurcation, and large adjacent branches may be markers for increased complications. Proximal tortuosity in the ICA or VA is one of the most important angiographic features that can predict success or failure. Although self-expanding cerebral stents have somewhat mitigated the inability to deliver devices, tortuosity can be extreme, and even delivery of a small balloon catheter can be very difficult and delivery of balloon-mounted stents even more challenging and risky.¹⁵³ The author's approach is to avoid EVT altogether if it is not likely that a stent can be safely delivered even if angioplasty appears feasible because of the risk of complications that could require provisional stenting.

Clinical Manifestations

Ischemic stroke and TIA are the most common presentations for ICAD, although most patients are likely asymptomatic. The symptoms vary based on the vessel involved, as already discussed. Stroke is typically, but not always, heralded by TIA, which can be stereotyped.^{154,155} Ischemia can result from hemodynamic compromise as discussed earlier, but artery-artery embolization is also common and may also be transient or recurrent.^{154,156} In addition to involvement of the large artery territories, stenoses of the MCA or BA can cause symptoms because of atherosclerotic involvement of the origins of perforators which can mimic lacunar strokes clinically and on imaging.¹⁵⁷ A combination of hemodynamic compromise and microembolization can also occur, causing a unique pattern on MRI and is called the "impaired washout of emboli" theory.¹⁵⁸ Rarely, SAH may be the first manifestation of ICAD. These are typically on the cerebral convexity rather than in the basal cisterns and fissures as would be expected from aneurysmal SAH. MRI typically shows a small infarct in the cortex underneath the SAH.

Techniques

The approach to these patients is based on a few fundamental principles. First is the establishment of supportive access to the vessel being treated. Second, adequate pretreatment with DAPT (aspirin and clopidogrel) is essential, and the author strongly advocates for assessment of adequate platelet inhibition or genetic testing to exclude poor metabolizers of clopidogrel. Poor response to aspirin also occurs, and it is the author's approach based on unpublished data to adjust dosing of either agent to achieve therapeutic platelet inhibition. It is important to remember that even microemboli can be symptomatic in the brain, and acute stent thrombosis may be very difficult to manage, especially if stent delivery was challenging to begin with.¹⁵⁹ Ticagrelor is a reasonable alternative and has FDA indications for the treatment of patients with stroke, but in the author's anecdotal experience, it typically results in nearly complete platelet inhibition, raising the concern of an increased risk of ICH, particularly in patients at risk of the cerebral hyperperfusion syndrome (HPS; see later); it should therefore be used very judiciously until prospective data confirm its safety in this unique circumstance. A single antiplatelet, typically aspirin, can be used if balloon angioplasty

alone is performed. Third, a “less is more” approach may be the safest approach. This is particularly relevant in device sizing due to the fragility of the intradural vessels and the presence of multiple perforators.

As with acute stroke, the interventionist should already have a planned approach based on the results of CTA or MRA. Complete six-vessel DSA may sometimes be needed to fully understand the hemodynamics and potential sources for collateral flow and to exclude other pathologies, especially vasculitis, which should be considered a contraindication to EVT because of the very high risk of vessel rupture. Angiography should delineate all branches in the diseased segment, and a decision should be made as to which branch may be safely compromised in the case of “snowplowing” or stenting across the ostium; the latter is important in case the patient experiences a stroke and access to that branch is required. Coronary techniques such as y-stenting, kissing balloons and stents, and so on may be associated with a high risk of vessel perforation and death.

A femoral approach is easiest for MCA and ICA procedures as well as VB interventions, but radial access should be considered for the latter, especially if there is severe arch, innominate, subclavian, or VA angulation. A therapeutic activated clotting time in the 250-second range should be achieved with unfractionated heparin. GP IIb/IIIa receptor antagonists should be available for bailout in case of acute stent thrombosis but should not be used routinely. A supportive 6-Fr guide catheter (e.g., Envoy XB, Codman & Shurtleff, Inc.) should be placed distally in the cervical ICA or distal V2 segment of the VA if safe and feasible. Alternatively, a 6- to 8-Fr sheath can be placed in the common or proximal internal carotid or subclavian arteries for more support, or a combination sheath guide (e.g., Neuron-Max, Penumbra, Inc.) can also be used. The latter behaves like a sheath proximally but has excellent flexibility and can be delivered distally like a guide catheter. An intermediate catheter or guide extender can also be used in cases of severe tortuosity.

A soft microwire with an atraumatic tip such as a Synchro (Stryker Inc.) should be chosen. Medium or stiff wires should be avoided for intracranial work, although occasionally, an exchange for a middle-weight supportive wire may be necessary. In these cases, the wire tip should be kept as proximal as possible to decrease the risk of wire perforation. As described in the acute stroke section, wires should be advanced with great care to avoid smaller branches and perforators. Advanced biplane roadmapping is particularly helpful in this regard. The operator must be continually on the lookout for wire-tip migration, emboli, branch occlusions, dissection, and perforation. This is best accomplished with an awake patient who can report headache or the occurrence of neurologic deficits.^{147,160} Headache is an important marker for traction on the cerebral vessels, can portend impending vessel injury and perforation, and should trigger an immediate assessment of the angiographic images for malposition of devices.¹⁴⁷

The author prefers over-the-wire rather than rapid exchange systems. This is because the former allow for the exchange of wires if needed without having to recross lesions. Also, if there is thrombosis requiring MT, the longer wire will permit exchanging for a distal aspiration catheter

(especially if a stent has already been placed) or a microcatheter to allow delivery of a stent retriever (contraindicated if a stent was deployed).

Because no RCTs have showed the superiority of stenting over angioplasty in the intracranial vessels, stenting has generally been preferred for the same reasons that it is preferred in the coronary arteries. Still, angioplasty may sometimes be sufficient, and the safest approach is to predilate the lesion with an undersized balloon (~85% of the expected normal vessel size); this is important because oversizing or even sizing 1:1 can lead to vessel injury and rupture (Figure 25.3).¹⁵² Predilation can assist with adequate sizing and determines the lesion response to angioplasty and stretching of the vessels (i.e., headache). If a submaximal balloon inflation causes severe headache, then the patient's vessel may not tolerate larger devices, including stents; this can also indicate that the balloon inflation rate was too fast.¹⁴⁷ After submaximal angioplasty, a vasodilator should be considered (e.g., NTG 200–400 μ g given intraarterially) before angiography to treat any vasospasm that may falsely make the vessel smaller than it really is. At this stage, the patient is examined, and if there is no neurologic deficit and a greater than 30% residual stenosis, then a decision will need to be made as to whether to proceed with stenting. Waiting 10 to 15 minutes and repeating the angiogram can sometimes be very helpful to monitor for early recoil. Stenting may be obviated if the result is satisfactory, especially if the vessel is very small (<2.25 mm), because drug-eluting stents are not available in these sizes, and restenosis risk is very high in such vessels with or without stenting.

If the result is suboptimal, then stenting can be considered. Three stents have been developed specifically for the treatment of patients with ICAD. The balloon-expandable NeuroLink (Guidant Corp.) stent was studied in the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLIVA) trial, but this study had only 43 patients, and this device is not commercially available.¹⁶¹ The more recent device, the Wingspan system (Stryker Inc.), is a self-expanding nitinol, highly flexible, and deliverable stent that is marketed with a balloon system (Gateway). This system is available under an FDA Humanitarian Device Exemption¹⁶² for the treatment of patients with ICAD. The third device was a balloon-expandable stent (Pharos Vitesse, Codman & Shurtleff, Inc.) that is not commercially available after a failed clinical trial.¹⁶³ An alternative is to use the latest generation of drug-eluting coronary stents (DESs). This approach is off label but the author and others have been using DESs since their first introduction into the US market experience with good results.^{164,165}

Balloon-mounted stents should be sized based on the smallest segment into which they will be delivered, and if there is a large difference in the size of the parent vessel and the branch to be stented, then a self-expanding stent should be strongly considered. The latter is typically oversized by 0.5 to 1 mm or even larger and is ideal for the ICA terminus or the VB junction. The Wingspan delivery system requires a continuous flush at the proximal hub and is only available as an over-the-wire system. The nose cone on the delivery catheter is somewhat stiff but is generally less stiff than a

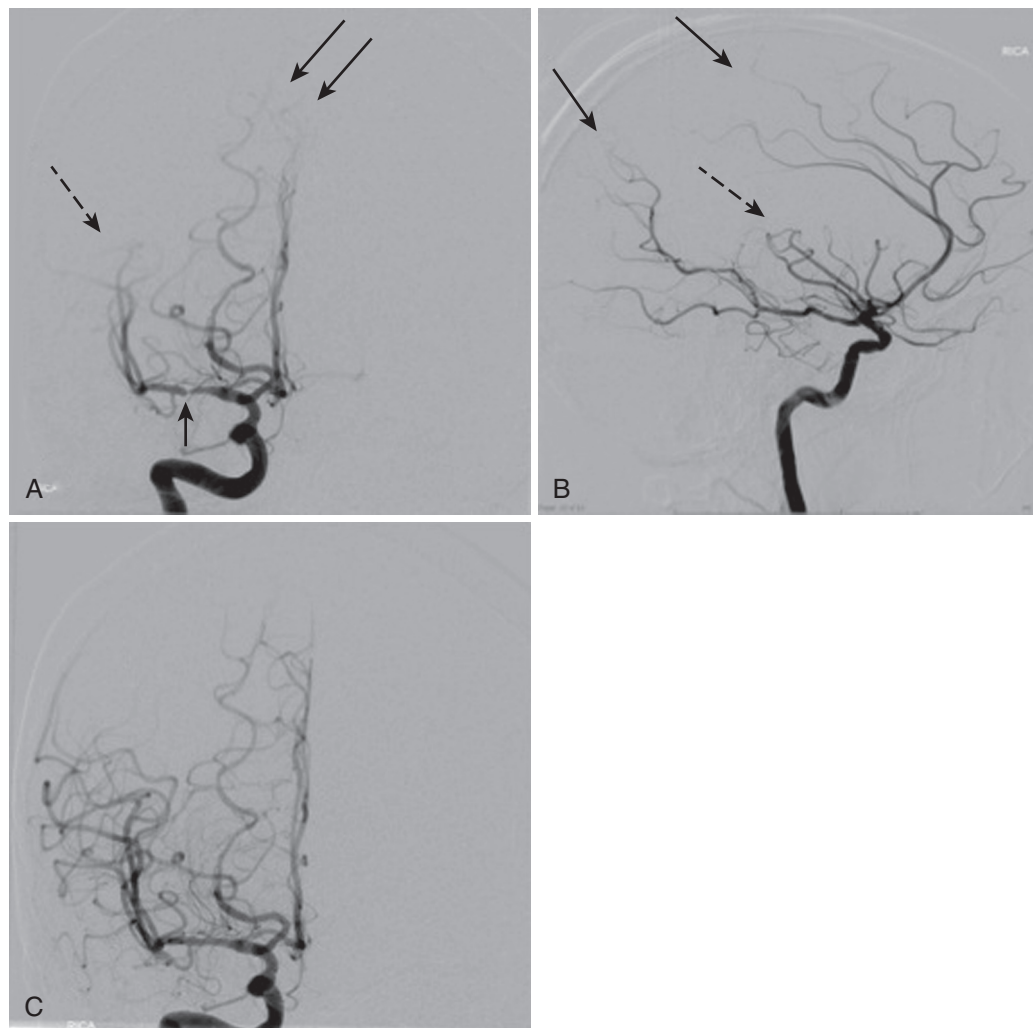


FIGURE 25.3 A selective right internal carotid angiogram in the anteroposterior (A) and lateral (B) projections demonstrates a severe middle cerebral artery stenosis (*short arrow*). The middle cerebral artery cortical branches (*dashed arrow*) fill slower than the anterior cerebral and (fetal) posterior cerebral artery branches (*solid arrows*), indicating severe flow limitation. After stenting with a 2.75-mm stent, there is normalization of antegrade flow (C) with a marked but incomplete normalization of the vessel lumen.

balloon-mounted stent.¹⁶⁰ The system should be advanced over the wire past the lesion and then withdrawn into position because of its tendency to jump forward if there is redundancy proximally. The stent is then carefully unsheathed in position, and it cannot be recaptured after it starts to be deployed; therefore, the user must be very familiar with the markers on the stent delivery system.

The current generation of coronary stents is highly deliverable even in the cerebral vasculature, although approximately 8% to 10% of the time, delivery is not possible.¹⁶⁵ The usual tricks of maintaining guide catheter support and exchanging for medium-support wires, buddy wires, and intermediate catheters can be helpful.¹⁶⁶

Postdilation may be needed if a self-expanding stent is used, particularly if there was a significant residual after angioplasty; the Wingspan has very little radial force. Occasionally, the lesion is densely calcified or severely fibrotic and may be resistant to angioplasty. Use of a non-compliant balloon can be considered if the lesion is not calcified, but the balloon must be slightly undersized. The safety of this approach is unknown, and great caution

should be used, adhering to the “less is more” principle. Very calcified lesions should generally be avoided and definitely should not be treated aggressively because of their potential for dissection and perforation. It may be preferable to leave behind a residual stenosis rather than taking the risk of a perforation; restenosis, whether after angioplasty alone or within a stent, is typically easier to deal with.

After an adequate result has been achieved, the patient should be examined, followed by control angiography including the entire cerebral vasculature. The angiograms should be reviewed for subtle dissection, emboli, and evidence of extravasation. The latter can be difficult to see and may not manifest clinically; scrutiny of the vessel segment where the wire tip was parked is the most critical. Embolism, thrombosis, and dissection are the most common causes of ischemia during EVT, but ICH is the most feared complication; although vasospasm may also occur, it is rarely symptomatic. If the patient develops a neurologic deficit intraprocedurally, the operator should immediately perform an angiogram of the likely

culprit vessel in multiple orthogonal planes, which should then be reviewed closely, as described earlier. If an LVO is noted, then EVT must be rapidly performed following the approach described earlier, remembering that the stent retrievers should be avoided if a stent was placed unless the occlusion is in another vessel, and fibrinolytics and GP IIb/IIIa antagonists may be used but with extreme caution in those with recent stroke or profound hypertension because of the risk of HPS, which can lead to fatal ICH.¹⁶⁸⁻¹⁶⁹

If there is neurologic deterioration and immediate angiography does not reveal an LVO, then an expanding ICH should be suspected, and intraoperative CT should be performed immediately. While setting up for the CT, any heparin should be immediately reversed, and platelet and cryoprecipitate transfusions should be ordered immediately. If there is obvious extravasation of contrast on angiography, then the blood pressure should be dropped as quickly as possible, and preparations should be made for securing the airway and dealing with emesis. Along with heparin reversal and transfusion of platelets, balloon tamponade should be considered, either directly at the site of the extravasation or more proximally if the bleeding vessel is too small. If this is ineffective, then therapeutic embolization and vessel sacrifice may be necessary to save the patient's life. Urgent neurosurgical consultation should also be requested in case hydrocephalus develops or there is a large hematoma causing mass effect with a risk of cerebral herniation. A formal CT scan may need to be performed as soon as the patient is stabilized. Despite all of these measures, it is unlikely the patient will survive if there is significant bleeding; furthermore, DAPT will likely need to be discontinued for days or longer, greatly increasing the risk of stent thrombosis and massive ischemic stroke.¹⁷⁰ The neurologic deterioration may occur in the few hours after the procedure. Under these circumstances, acute stent or vessel thrombosis caused by inadequate platelet inhibition and wire perforation, causing a slowly expanding hematoma are the most likely causes. Urgent CT of the brain will be needed, and all of the measures discussed above should be initiated depending on the cause.

The cerebral HPS is a unique condition that affects individuals who undergo any cerebral revascularization procedure, either surgical or endovascular. It is caused by disordered autoregulation that, as the name implies, leads to excessive cerebral blood flow that can result in endothelial and blood-brain barrier injury and eventually ICH and death.^{167,169} The risk factors for HPS are severe flow-limiting stenosis, poor collateral flow, recent stroke, and hypertension. Blood pressure control is the most important tool for the prevention and treatment of HPS after it develops.¹⁷¹ Even normal pressures may be relatively "high" for some patients, and very low systolic pressures (i.e., 80s and 90s) may be needed to alleviate the migraine-like headache that can be the prelude to ICH. Seizures, cerebral edema, and confusion may also be caused by HPS, and they peak at 3 to 5 days after the procedure.

As with AIS patients treated with MT, close observation, and blood pressure control in a stroke unit or neurologic intensive care unit are important. DAPT should be continued

for a minimum of 90 days if a Wingspan stent is placed and longer if a DES is used; this was the regimen in the SAMMPRIS trial.¹⁴⁵ The author's approach is to continue DAPT for 6 months and then to perform DSA to assess for restenosis. Depending on the type of DES, a decision can then be made regarding switching to a single agent.¹⁶⁵ There is a lack of long-term safety data for DAPT, which has been associated with an increased risk of ICH in patients with cerebrovascular disease.¹⁷²⁻¹⁷⁴

Clinical Outcomes

Much of the available outcomes data are from retrospective series of patients treated with a variety of techniques and devices. Those outcomes varied greatly with 30-day stroke, ICH, and death rates of 8% to 20%.^{142,147,151,152,164,174-185}

The most cited RCT of intracranial stenting was the SAMMPRIS trial.¹⁴⁵ A total of 451 patients with recently symptomatic 70% to 99% stenoses were randomized to MMT or MMT plus angioplasty and stenting with the Wingspan stent system. MMT consisted of aspirin 325 mg and clopidogrel 75 mg/day for 3 months, rosuvastatin (target low density lipoprotein <70mg/dL), systolic blood pressure control to below 140 mm Hg (<130 mm Hg for patients with diabetes), and lifestyle modification and coaching. The study was terminated early after a preplanned interim analysis that showed worse outcomes in the stenting plus MMT arm compared with the MMT arm. The 30-day stroke and death rates were 14.7% in the treatment group compared with 5.8% with MMT ($P = .002$).¹⁴⁵ Based on these results, there was immediate reduction in EVT for ICAD, which has not changed substantially in the years since publication of the trial. SAMMPRIS had significant limitations, including (1) inclusion of patients who had not failed MMT; (2) many of the operators had minimal experience with the treatment of patients with ICAD or with the Wingspan stent; (3) patients were selected only by angiographic criteria and not by hemodynamic compromise, which was not assessed in the trial; (4) the trial did not distinguish between perforator stroke and distal territory ischemia; and (5) the procedures were performed with general anesthesia and combined with some other procedural requirements, resulted in a high-rate of wire perforations and ICH.^{146,186}

The Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) trial suffered from similar limitations and was stopped early in 2014 because of futility.¹⁶³ A total of 112 patients were randomized to MMT or MMT plus stenting with the balloon-expandable Pharos Vitesse stent, which had been designed for ICAD. The 30-day periprocedural event rates were 9.4% with MMT versus 24.1% with stenting with an ICH rate of 0% versus 8.6%.

These results were significantly worse than those reported in a large multinational registry of angioplasty and stenting of 670 lesions in 637 patients.¹⁵³ The majority of patients (68%) were treated with balloon-expandable rather than self-expanding stents. The 30-day periprocedural stroke and death rate was similar (6.1%) between both stent types. Treatment within 24 hours of the index event (OR, 4.0, 95% CI, 1.7–6.7; $P < .007$) was associated with the risk of complications. Treatment of focal lesions

was associated with fewer events (OR, 0.31; 95% CI, 0.13–0.72; $P < .001$), and the restenosis risk was lower in patients treated with balloon-expandable (20%) versus self-expanding stents (28%).

Taking the lessons learned from SAMMPRIS and VISSIT, the Wingspan Stent System Post Market Surveillance (WEAVE) trial was designed. This was a prospective postmarket surveillance study mandated by the FDA. All patients were treated per FDA on-label criteria for the Wingspan stent, which mandated failure of MMT and treatment for 8 days or more since the last stroke.¹⁸⁷ Operators were experienced with the system. A total of 152 patients were treated before the trial was stopped early because of a much lower than expected (2.6%) rate of stroke, ICH, or death. One-year follow-up data were available for 129 patients, and including the periprocedural event rate, the 1-year rate of delayed stroke or death was 8.5%, which was almost half of the 30-day event rate in SAMMPRIS.¹⁸⁸

Very long-term follow-up data are lacking. The author and his colleagues collected follow-up data on 53 patients with 69 arterial lesions who were followed for up to 7 years (median, 24 months). They were treated with angioplasty, bare-metal stents, or DESs.¹⁶⁵ In this consecutive series, the 30-day death or stroke rate was 10.1%, with only 1 death.

At 2 years, the cumulative stroke/death/TIA rate was 15.9%. The risk of restenosis was 15.9% at 1 year, and only 18.2% were symptomatic. The risk of restenosis was associated with vessel size smaller than 2.5 mm (HR, 4.78; 95% CI, 1.35–16.93) and emergent interventions for AIS (HR, 6.36; 95% CI, 1.78–22.56).

CONCLUSIONS

Acute ischemic stroke caused by LVO can be effectively treated, in appropriately selected patients, with MT out to 24 hours. The latest MT devices are very safe but have not been definitively validated in patients with VB stroke or pediatric patients. Emergent angioplasty and stenting can be considered in selected patients with atherosclerotic occlusion. Intracranial angioplasty and stenting remains investigational and should be reserved for carefully selected patients who have failed medical therapy and who are more than 7 days from their last stroke and only after thorough evaluation of their clinical presentation, vascular anatomy, and the presence of impaired cerebrovascular reserve. Many unanswered questions remain regarding both types of procedures.

Visit Elsevier eBooks+ to access the complete list of references.

SELECTED REFERENCES

1. Tsao CW, Aday AW, Almarazooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation*. 2022;145(8):e153-e639.
5. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35-41.
7. Abou-Chebl A, Steinmetz H. Critique of “stenting versus aggressive medical therapy for intracranial arterial stenosis” by Chimowitz et al in the *New England Journal of Medicine*. *Stroke*. 2012;43(2):616-620.
18. Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(10):3020-3035.
19. Mayer SA, Viarasilpa T, Panyavachiraporn N, et al. CTA-for-All: impact of emergency computed tomographic angiography for all patients with stroke presenting within 24 hours of onset. *Stroke*. 2020;51(1):331-334.
21. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378(8):708-718.
24. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333(24):1581-1587.
31. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingle R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke*. 2011;42(6):1775-1777.
35. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr, American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke*. 2009;40(8):2945-2948.
39. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418.
40. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378(1):11-21.
41. Nguyen TN, Abdalkader M, Nagel S, et al. Noncontrast computed tomography vs computed tomography perfusion or magnetic resonance imaging selection in late presentation of stroke with large-vessel occlusion. *JAMA Neurol*. 2022;79(1):22-31.
44. Campbell BC, Mitchell PJ, Yan B, et al. A multicenter, randomized, controlled study to investigate EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy (EXTEND-IA). *Int J Stroke*. 2014;9(1):126-132.
45. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372(24):2285-2295.
46. Hill MD, Rowley HA, Adler F, et al. Selection of acute ischemic stroke patients for intra-arterial thrombolysis with pro-urokinase by using ASPECTS. *Stroke*. 2003;34(8):1925-1931.
50. Eljovich L, Dornbos D III, Nickele C, et al. Automated emergent large vessel occlusion detection by artificial intelligence improves stroke workflow in a hub and spoke stroke system of care. *J Neurointerv Surg*. 2022;14(7):704-708.
55. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723-1731.
57. Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316(12):1279-1288.
59. Liebeskind DS, Tomsick TA, Foster LD, et al. Collaterals at angiography and outcomes in the Interventional Management of Stroke (IMS) III trial. *Stroke*. 2014;45(3):759-764.
72. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA*. 1999;282(21):2003-2011.
77. Campbell BC, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before endovascular thrombectomy (EXTEND-IA TNK): a multicenter, randomized, controlled study. *Int J Stroke*. 2018;13(3):328-334.
81. Abou-Chebl A, Bajzer CT, Krieger DW, Furlan AJ, Yadav JS. Multimodal therapy for the treatment of severe ischemic stroke combining GPIIb/IIIa antagonists and angioplasty after failure of thrombolysis. *Stroke*. 2005;36(10):2286-2288.
90. Nguyen TN, Malisch T, Castonguay AC, et al. Balloon guide catheter improves revascularization and clinical outcomes with the Solitaire device: analysis of the North American Solitaire Acute Stroke Registry. *Stroke*. 2013;45(1):141-145.
92. Linfante I, Starosciak AK, Walker GR, et al. Predictors of poor outcome despite recanalization: a multiple regression analysis of the NASA registry. *J Neurointerv Surg*. 2016;8(3):224-229.
94. Zaidat OO, Castonguay AC, Linfante I, et al. First pass effect: a new measure for stroke thrombectomy devices. *Stroke*. 2018;49(3):660-666.
95. Lapergue B, Blanc R, Costalat V, et al. Effect of thrombectomy with combined contact aspiration and stent retriever vs stent retriever alone on revascularization in patients with acute ischemic stroke and large vessel occlusion: the ASTER2 randomized clinical trial. *JAMA*. 2021;326(12):1158-1169.
96. Smith ER, Bethel JA, Smith TB, et al. Stent retriever versus direct aspiration thrombectomy for acute large vessel occlusion: a meta-analysis including 17,556 patients, from MR CLEAN to present. *Clin Neurol Neurosurg*. 2022;213:107122.
103. Zaidat OO, Wolfe T, Hussain SI, et al. Interventional acute ischemic stroke therapy with intracranial self-expanding stent. *Stroke*. 2008;39(8):2392-2395.
104. Abou-Chebl A, Vora N, Yadav JS. Safety of angioplasty and stenting without thrombolysis for the treatment of early ischemic stroke. *J Neuroimaging*. 2009;19(2):139-143.
105. Jovin TG, Gupta R, Uchino K, et al. Emergent stenting of extracranial internal carotid artery occlusion in acute stroke has a high revascularization rate. *Stroke*. 2005;36(11):2426-2430.
118. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11-20.
119. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019-1030.
121. McDowell MM, Ducruet AF. Time is brain: a critical analysis of the EXTEND-IA and ESCAPE trials. *World Neurosurg*. 2015;83(6):949-951.
124. Chen J, Wan T-F, Xu T-C, Chang G-C, Chen H-S, Liu L. Direct endovascular thrombectomy or with prior intravenous thrombolysis for acute ischemic stroke: a meta-analysis. *Front Neurol*. 2021;12:752698.
125. Abou-Chebl A. Endovascular treatment of acute ischemic stroke may be safely performed with no time window limit in appropriately selected patients. *Stroke*. 2010;41(9):1996-2000.
127. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49(3):e46-e110.
128. Abou-Chebl A, Lin R, Hussain MS, et al. Conscious sedation versus general anesthesia during endovascular therapy for acute anterior circulation stroke: preliminary results from a retrospective, multicenter study. *Stroke*. 2010;41(6):1175-1179.
132. Abou-Chebl A, Yeatts SD, Yan B, et al. Impact of general anesthesia on safety and outcomes in the endovascular arm of Interventional Management of Stroke (IMS) III Trial. *Stroke*. 2015;46(8):2142-2148.
134. Brinjikji W, Pasternak J, Murad MH, et al. Anesthesia-related outcomes for endovascular stroke revascularization: a systematic review and meta-analysis. *Stroke*. 2017;48(10):2784-2791.
145. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med*. 2011;365(11):993-1003.
146. Abou-Chebl A, Steinmetz H. Critique of “stenting versus aggressive medical therapy for intracranial arterial stenosis” by Chimowitz et al in the *New England Journal of Medicine*. *Stroke*. 2012;43(2):616-620.
148. Liebeskind DS, Cotsonis GA, Saver JL, et al. Collaterals dramatically alter stroke risk in intracranial atherosclerosis. *Ann Neurol*. 2011;69(6):963-974.
153. Jiang W-J, Cheng-Ching E, Abou-Chebl A, et al. Multicenter analysis of stenting in symptomatic intracranial atherosclerosis. *Neurosurgery*. 2012;70(1):25-30.
158. Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. *Arch Neurol*. 1998;55(11):1475-1482.
164. Abou-Chebl A, Bashir Q, Yadav JS. Drug-eluting stents for the treatment of intracranial atherosclerosis: initial experience and midterm angiographic follow-up. *Stroke*. 2005;36(12):e165-e168.
169. Abou-Chebl A, Yadav JS, Reginelli JP, Bajzer C, Bhatt D, Krieger DW. Intracranial hemorrhage and hyperperfusion syndrome following carotid artery stenting: risk factors, prevention, and treatment. *J Am Coll Cardiol*. 2004;43(9):1596-1601.
171. Abou-Chebl A, Reginelli J, Bajzer CT, Yadav JS. Intensive treatment of hypertension decreases the risk of hyperperfusion and intracerebral hemorrhage following carotid artery stenting. *Catheter Cardiovasc Interv*. 2007;69(5):690-696.
173. Bhatt DL, Flather MD, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol*. 2007;49(19):1982-1988.
176. Abou-Chebl A, Krieger DW, Bajzer CT, Yadav JS. Intracranial angioplasty and stenting in the awake patient. *Stroke*. 2006;16(3):216-223.
187. Alexander MJ, Zauner A, Chaloupka JC, et al. WEAVE trial: final results in 152 on-label patients. *J Neuroimaging*. 2019;50(4):889-894.
188. Alexander MJ, Zauner A, Gupta R, et al. The WOVEN trial: Wingspan one-year vascular events and neurologic outcomes. *J Neurointerv Surg*. 2021;13(4):307-310.

REFERENCES

1. Tsao CW, Aday AW, Almarazooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation*. 2022;145(8):e153-e639.
2. Lloyd-Jones D, Adams RJ, Brown TM, et al. Executive summary: heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*. 2010;121(7):948-954.
3. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation*. 2011;123(4):e18-e209.
4. Sacco RL, Boden-Albala B, Gan R, et al. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. *Am J Epidemiol*. 1998;147(3):259-268.
5. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke*. 1993;24(1):35-41.
6. Arnold M, Halpern M, Meier N, et al. Age-dependent differences in demographics, risk factors, co-morbidity, etiology, management, and clinical outcome of acute ischemic stroke. *J Neurol*. 2008;255(10):1503-1507.
7. Abou-Chebl A, Steinmetz H. Critique of "stenting versus aggressive medical therapy for intracranial arterial stenosis" by Chimowitz et al in the *New England Journal of Medicine*. *Stroke*. 2012;43(2):616-620.
8. Connolly ES Jr, Rabenstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 2012;43(6):1711-1737.
9. Mohr JP, Caplan LR, Melski JW, et al. The Harvard Cooperative Stroke Registry: a prospective registry. *Neurology*. 1978;28(8):754-762.
10. Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet*. 2005;366(9479):29-36.
11. Johnston SC. Short-term prognosis after a TIA: a simple score predicts risk. *Cleve Clin J Med*. 2007;74(10):729-736.
12. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009;40(6):2276-2293.
13. Johnston SC, Albers GW, Gorelick PB, et al. National Stroke Association recommendations for systems of care for transient ischemic attack. *Ann Neurol*. 2011;69(5):872-877.
14. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(1):227-276.
15. Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38(5):1655-1711.
16. Broderick JP, Adams HP Jr, Barsan W, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 1999;30(4):905-915.
17. Adams HP Jr, Brott TG, Furlan AJ, et al. Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Circulation*. 1996;94(5):1167-1174.
18. Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(10):3020-3035.
19. Mayer SA, Viarasilpa T, Panyavachiraporn N, et al. CTA-for-all: impact of emergency computed tomographic angiography for all patients with stroke presenting within 24 hours of onset. *Stroke*. 2020;51(1):331-334.
20. Albers GW, Thijs VN, Wechsler L, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Ann Neurol*. 2006;60(5):508-517.
21. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378(8):708-718.
22. Li Q, Li J, Lv F, Li K, Luo T, Xie P. A multidetector CT angiography study of variations in the circle of Willis in a Chinese population. *J Clin Neurosci*. 2011;18(3):379-383.
23. Macchi C, Lova RM, Miniati B, et al. The circle of Willis in healthy older persons. *J Cardiovasc Surg*. 2002;43(6):887-890.
24. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333(24):1581-1587.
25. Hsia AW, Edwards DF, Morgenstern LB, et al. Racial disparities in tissue plasminogen activator treatment rate for stroke: a population-based study. *Stroke*. 2011;42(8):2217-2221.
26. Eissa A, Krass I, Bajorek BV. Optimizing the management of acute ischaemic stroke: a review of the utilization of intravenous recombinant tissue plasminogen activator (tPA). *J Clin Pharm Ther*. 2012;37(6):620-629.
27. Kleindorfer D, Lindsell CJ, Brass L, Koroshetz W, Broderick JP. National US estimates of recombinant tissue plasminogen activator use: ICD-9 codes substantially underestimate. *Stroke*. 2008;39(3):924-928.
28. Katzan IL, Hammer MD, Hixson ED, Furlan AJ, Abou-Chebl A, Nadzam DM. Utilization of intravenous tissue plasminogen activator for acute ischemic stroke. *Arch Neurol*. 2004;61(3):346-350.
29. Wolpert SM, Bruckmann H, Greenlee R, Wechsler L, Pessin MS, del Zoppo GJ. Neurologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA Acute Stroke Study Group. *AJNR Am J Neuroradiol*. 1993;14(1):3-13.
30. Saqqur M, Uchino K, Demchuk AM, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke*. 2007;38(3):948-954.
31. Riedel CH, Zimmermann P, Jensen-Kondering U, Stinge R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke*. 2011;42(6):1775-1777.
32. Saver JL, Yafeh B. Confirmation of tPA treatment effect by baseline severity-adjusted end point reanalysis of the NINDS-tPA stroke trials. *Stroke*. 2007;38(2):414-416.
33. Kharitonova T, Ahmed N, Thorén M, et al. Hyperdense middle cerebral artery sign on admission CT scan—prognostic significance for ischemic stroke patients treated with intravenous thrombolysis in the safe implementation of thrombolysis in Stroke International Stroke Thrombolysis Register. *Cerebrovasc Dis*. 2009;27(1):51-59.
34. De Silva DA, Brekenfeld C, Ebinger M, et al. The benefits of intravenous thrombolysis relate to the site of baseline arterial occlusion in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET). *Stroke*. 2010;41(2):295-299.
35. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr, American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke*. 2009;40(8):2945-2948.
36. Mattie HP, Arnold M, Georgiadis D, et al. Comparison of intraarterial and intravenous thrombolysis for ischemic stroke with hyperdense middle cerebral artery sign. *Stroke*. 2008;39(2):379-383.
37. Katzan IL, Furlan AJ, Lloyd LE, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA*. 2000;283(9):1151-1158.
38. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870-947.
39. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418.
40. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378(1):11-21.
41. Nguyen TN, Abdalkader M, Nagel S, et al. Noncontrast computed tomography vs computed tomography perfusion or magnetic resonance imaging selection in late presentation of stroke with large-vessel occlusion. *JAMA Neurol*. 2022;79(1):22-31.
42. Lansberg MG, Straka M, Kemp S, et al. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. *Lancet Neurol*. 2012;11(10):860-867.
43. Schaefer PW, Barak ER, Kamalian S, et al. Quantitative assessment of core/penumbra mismatch in acute stroke: CT and MR perfusion imaging are strongly correlated when sufficient brain volume is imaged. *Stroke*. 2008;39(11):2986-2992.
44. Campbell BC, Mitchell PJ, Yan B, et al. A multicenter, randomized, controlled study to investigate EXTending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy (EXTEND-IA). *Int J Stroke*. 2014;9(1):126-132.
45. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372(24):2285-2295.
46. Hill MD, Rowley HA, Adler F, et al. Selection of acute ischemic stroke patients for intra-arterial thrombolysis with pro-urokinase by using ASPECTS. *Stroke*. 2003;34(8):1925-1931.
47. Lansberg MG, Lee J, Christensen S, et al. RAPID automated patient selection for reperfusion therapy: a pooled analysis of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study. *Stroke*. 2011;42(6):1608-1614.
48. Rava RA, Snyder KV, Mokin M, et al. Assessment of a Bayesian Vitrea CT perfusion analysis to predict final infarct and penumbra volumes in patients

- with acute ischemic stroke: a comparison with RAPID. *AJNR Am J Neuroradiol.* 2020;41(2):206-212.
49. Bouslama M, Ravindran K, Harston G, et al. Noncontrast computed tomography e-Stroke infarct volume is similar to RAPID computed tomography perfusion in estimating postperfusion infarct volumes. *Stroke.* 2021;52(2):634-641.
50. Eljovich L, Dornbos D III, Nickele C, et al. Automated emergent large vessel occlusion detection by artificial intelligence improves stroke workflow in a hub and spoke stroke system of care. *J Neurointerv Surg.* 2022;14(7):704-708.
51. Jahan R, Liebeskind DS, Zaidat OO, Mueller-Kronast NH, Froehler MT, Saver JL. Stent retriever thrombectomy for anterior vs. posterior circulation ischemic stroke: analysis of the STRATIS registry. *Front Neurol.* 2021;12:706130.
52. Sommer P, Scharer S, Posekany A, et al. Thrombectomy in basilar artery occlusion. *Int J Stroke.* 2022;17(9):1006-1012.
53. Jovin TG, Yonas H, Gebel JM, et al. The cortical ischemic core and not the consistently present penumbra is a determinant of clinical outcome in acute middle cerebral artery occlusion. *Stroke.* 2003;34(10):2426-2433.
54. Nogueira RG, Smith WS. Safety and efficacy of endovascular thrombectomy in patients with abnormal hemostasis: pooled analysis of the MERCI and Multi MERCI trials. *Stroke.* 2009;40(2):516-522.
55. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387(10029):1723-1731.
56. Janssen PM, van Overhagen K, Vinklárek J, et al. Between-center variation in outcome after endovascular treatment of acute stroke: analysis of two nationwide registries. *Circ Cardiovasc Qual Outcomes.* 2022;15(3):e008180.
57. Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA.* 2016;316(12):1279-1288.
58. Ribo M, Flores A, Rubiera M, et al. Extending the time window for endovascular procedures according to collateral pial circulation. *Stroke.* 2011;42(12):3465-3469.
59. Liebeskind DS, Tomsick TA, Foster LD, et al. Collaterals at angiography and outcomes in the Interventional Management of Stroke (IMS) III trial. *Stroke.* 2014;45(3):759-764.
60. Kim JJ, Fischbein NJ, Lu Y, Pham D, Dillon WP. Regional angiographic grading system for collateral flow: correlation with cerebral infarction in patients with middle cerebral artery occlusion. *Stroke.* 2004;35(6):1340-1344.
61. Khatri P, Broderick JP, Khoury JC, Carrozzella JA, Tomsick TA. Microcatheter contrast injections during intra-arterial thrombolysis may increase intracranial hemorrhage risk. *Stroke.* 2008;39(12):3283-3287.
62. Hommel M, Cornu C, Boutitie F, Boissel JP, Multicenter Acute Stroke Trial—Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med.* 1996;335(3):145-150.
63. Arnold M, Schroth G, Nedeltchev K, et al. Intra-arterial thrombolysis in 100 patients with acute stroke due to middle cerebral artery occlusion. *Stroke.* 2002;33(7):1828-1833.
64. Barnwell SL, Clark WM, Nguyen TT, O'Neill OR, Wynn ML, Coull BM. Safety and efficacy of delayed intraarterial urokinase therapy with mechanical clot disruption for thromboembolic stroke. *AJNR Am J Neuroradiol.* 1994;15(10):1817-1822.
65. Brekenfeld C, Remonda L, Nedeltchev K, et al. Endovascular neuroradiological treatment of acute ischemic stroke: techniques and results in 350 patients. *Neurol Res.* 2005;27(suppl 1):S29-S35.
66. Chang K-C, Hsu S-W, Liou C-W, et al. Intra-arterial thrombolytic therapy for acute intracranial large artery occlusive disease in patients selected by magnetic resonance image. *J Neurol Sci.* 2010;297(1-2):46-51.
67. Tountopoulou A, Ahl B, Weissenborn K, Becker H, Goetz F. Intra-arterial thrombolysis using rt-PA in patients with acute stroke due to vessel occlusion of anterior and/or posterior cerebral circulation. *Neuroradiology.* 2008;50(1):75-83.
68. Mandava P, Kent TA. Intra-arterial therapies for acute ischemic stroke. *Neurology.* 2007;68(24):2132-2139.
69. Del Zoppo GJ, Ferbert A, Otis S, et al. Local intra-arterial fibrinolytic therapy in acute carotid territory stroke. A pilot study. *Stroke.* 1988;19(3):307-313.
70. Qureshi AI, Harris-Lane P, Kirmani JF, et al. Intra-arterial reteplase and intravenous abciximab in patients with acute ischemic stroke: an open-label, dose-ranging, phase I study. *Neurosurgery.* 2006;59(4):789-796.
71. Qureshi AI, Ali Z, Suri MF, et al. Intra-arterial third-generation recombinant tissue plasminogen activator (reteplase) for acute ischemic stroke. *Neurosurgery.* 2001;49(1):41-48.
72. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial pro-urokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *Prolyse in Acute Cerebral Thromboembolism.* *JAMA.* 1999;282(21):2003-2011.
73. Del Zoppo GJ, Higashida RT, Furlan AJ, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. *Stroke.* 1998;29(1):4-11.
74. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med.* 2013;368(10):893-903.
75. Renú A, Millán M, San Román LS, et al. Effect of intra-arterial alteplase vs placebo following successful thrombectomy on functional outcomes in patients with large vessel occlusion acute ischemic stroke: the CHOICE randomized clinical trial. *JAMA.* 2022;327(9):826-835.
76. Yokogami K, Nakano S, Ohta H, Goya T, Wakisaka S. Prediction of hemorrhagic complications after thrombolytic therapy for middle cerebral artery occlusion: value of pre- and post-therapeutic computed tomographic findings and angiographic occlusive site. *Neurosurgery.* 1996;39(6):1102-1107.
77. Campbell BC, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before endovascular thrombectomy (EXTEND-IA TNK): a multicenter, randomized, controlled study. *Int J Stroke.* 2018;13(3):328-334.
78. Campbell BC, Mitchell PJ, Churilov L, et al. Effect of intravenous tenecteplase dose on cerebral reperfusion before thrombectomy in patients with large vessel occlusion ischemic stroke: the EXTEND-IA TNK part 2 randomized clinical trial. *JAMA.* 2020;323(13):1257-1265.
79. Campbell BC, Mitchell PJ, Churilov L, et al. Determining the optimal dose of tenecteplase before endovascular therapy for ischemic stroke (EXTEND-IA TNK Part 2): a multicenter, randomized, controlled study. *Int J Stroke.* 2020;15(5):567-572.
80. Yogendrakumar V, Churilov L, Mitchell PJ, et al. Safety and efficacy of tenecteplase in older patients with large vessel occlusion: a pooled analysis of the EXTEND-IA TNK trials. *Neurology.* 2022;98(12):e1292-e1301.
81. Abou-Chebl A, Bajzer CT, Krieger DW, Furlan AJ, Yadav JS. Multimodal therapy for the treatment of severe ischemic stroke combining GPIIb/IIIa antagonists and angioplasty after failure of thrombolysis. *Stroke.* 2005;36(10):2286-2288.
82. Lee DH, Jo KD, Kim HG, et al. Local intraarterial urokinase thrombolysis of acute ischemic stroke with or without intravenous abciximab: a pilot study. *J Vasc Interv Radiol.* 2002;13(8):769-774.
83. Adams HP Jr, Effron MB, Torner J, et al. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). *Stroke.* 2008;39(1):87-99.
84. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke.* 2008;39(4):1205-1212.
85. Nogueira RG, Gupta R, Dávalos A. IMS-III and SYNTHESIS Expansion trials of endovascular therapy in acute ischemic stroke: how can we improve? *Stroke.* 2013;44(11):3272-3274.
86. Ribo M, Alvarez-Sabin J, Montaner J, et al. Temporal profile of recanalization after intravenous tissue plasminogen activator: selecting patients for rescue reperfusion techniques. *Stroke.* 2006;37(4):1000-1004.
87. Adusumilli G, Pederson JM, Hardy N, et al. Mechanical thrombectomy with and without intravenous tissue plasminogen activator for acute ischemic stroke: a systematic review and meta-analysis using nested knowledge. *Front Neurol.* 2021;12:759759.
88. Wikholm G. Mechanical intracranial embolectomy. A report of two cases. *Interv Neuroradiol.* 1998;4(2):159-164.
89. Chopko BW, Kerber C, Wong W, Georgy B. Transcatheter snare removal of acute middle cerebral artery thromboembolism: technical case report. *Neurosurgery.* 2000;46(6):1529-1531.
90. Nguyen TN, Malisch T, Castonguay AC, et al. Balloon guide catheter improves revascularization and clinical outcomes with the Solitaire device: analysis of the North American Solitaire Acute Stroke registry. *Stroke.* 2014;45(1):141-145.
91. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke.* 2005;36(7):1432-1438.
92. Linfante I, Starosciak AK, Walker GR, et al. Predictors of poor outcome despite recanalization: a multiple regression analysis of the NASA registry. *J Neurointerv Surg.* 2016;8(3):224-229.
93. Arturo Larco J, Abbasi M, Liu Y, et al. Per-pass analysis of recanalization and good neurological outcome in thrombectomy for stroke: systematic review and meta-analysis. *Interv Neuroradiol.* 2022;28(3):358-363.
94. Zaidat OO, Castonguay AC, Linfante I, et al. First pass effect: a new measure for stroke thrombectomy devices. *Stroke.* 2018;49(3):660-666.
95. Lapergue B, Blanc R, Costalat V, et al. Effect of thrombectomy with combined contact aspiration and stent retriever vs stent retriever alone on revascularization in patients with acute ischemic stroke and large vessel occlusion: the ASTER2 Randomized Clinical Trial. *JAMA.* 2021;326(12):1158-1169.
96. Smith ER, Bethel JA, Smith TB, et al. Stent retriever versus direct aspiration thrombectomy for acute large vessel occlusion: a meta-analysis including 17,556 patients, from MR CLEAN to present. *Clin Neurol Neurosurg.* 2022;213:107122.
97. Bernsen MLE, Bruggeman AAE, Brouwer J, et al. Aspiration versus stent retriever thrombectomy for posterior circulation stroke. *Stroke.* 2022;53(3):749-757.
98. Nakano S, Iseda T, Yoneyama T, Kawano H, Wakisaka S. Direct percutaneous transluminal angioplasty for acute middle cerebral artery trunk occlusion: an alternative option to intra-arterial thrombolysis. *Stroke.* 2002;33(12):2872-2876.
99. Yoneyama T, Nakano S, Kawano H, et al. Combined direct percutaneous transluminal angioplasty and low-dose native tissue plasminogen activator therapy for acute embolic middle cerebral artery trunk occlusion. *AJNR Am J Neuroradiol.* 2002;23(2):277-281.
100. Ringer AJ, Qureshi AI, Fessler RD, Guterman LR, Hopkins LN. Angioplasty of intracranial occlusion resistant to thrombolysis in acute ischemic stroke. *Neurosurgery.* 2001;48(6):1282-1288.
101. Qureshi AI, Siddiqui AM, Suri MF, et al. Aggressive mechanical clot disruption and low-dose intra-arterial third-generation thrombolytic agent for ischemic stroke: a prospective study. *Neurosurgery.* 2002;51(5):1319-1327.
102. Gupta R, Vora NA, Horowitz MB, et al. Multimodal reperfusion therapy for acute ischemic stroke: factors predicting vessel recanalization. *Stroke.* 2006;37(4):986-990.
103. Zaidat OO, Wolfe T, Hussain SI, et al. Interventional acute ischemic stroke therapy with intracranial self-expanding stent. *Stroke.* 2008;39(8):2392-2395.

104. Abou-Chebl A, Vora N, Yadav JS. Safety of angioplasty and stenting without thrombolysis for the treatment of early ischemic stroke. *J Neuroimaging*. 2009;19(2):139-143.
105. Jovin TG, Gupta R, Uchino K, et al. Emergent stenting of extracranial internal carotid artery occlusion in acute stroke has a high revascularization rate. *Stroke*. 2005;36(11):2426-2430.
106. Roth C, Papanagiotou P, Behnke S, et al. Stent-assisted mechanical recanalization for treatment of acute intracerebral artery occlusions. *Stroke*. 2010;41(11):2559-2567.
107. Papanagiotou P, Roth C, Walter S, et al. Carotid artery stenting in acute stroke. *J Am Coll Cardiol*. 2011;58(23):2363-2369.
108. Xavier AR, Tiwari A, Purai N, et al. Safety and efficacy of intracranial stenting for acute ischemic stroke beyond 8 h of symptom onset. *J Neurointerv Surg*. 2012;4(2):94-100.
109. Heck DV, Brown MD. Carotid stenting and intracranial thrombectomy for treatment of acute stroke due to tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage. *J Neurointerv Surg*. 2015;7(3):170-175.
110. Eker OF, Bühlmann M, Dargazanli C, et al. Endovascular treatment of atherosclerotic tandem occlusions in anterior circulation stroke: technical aspects and complications compared to isolated intracranial occlusions. *Front Neurol*. 2018;9:1046.
111. Venturini G, Vuolo L, Pracucci G, et al. Association between carotid artery dissection and vascular tortuosity: a case-control study. *Neuroradiology*. 2022;64(6):1127-1134.
112. Edgell RC, Abou-Chebl A, Yadav JS. Endovascular management of spontaneous carotid artery dissection. *J Vasc Surg*. 2005;42(5):854-860.
113. Cohen JE, Gomori JM, Grigoriadis S, et al. Intra-arterial thrombolysis and stent placement for traumatic carotid dissection with subsequent stroke: a combined, simultaneous endovascular approach. *J Neurol Sci*. 2008;269(1-2):172-175.
114. Marnat G, Bühlmann M, Eker OF, et al. Multicentric experience in distal-to-proximal revascularization of tandem occlusion stroke related to internal carotid artery dissection. *AJNR Am J Neuroradiol*. 2018;39(6):1093-1099.
115. Marnat G, Sibon I, Bourcier R, et al. Thrombolysis improves reperfusion and the clinical outcome in tandem occlusion stroke related to cervical dissection: TITAN and ETIS pooled analysis. *J Stroke*. 2021;23(3):411-419.
116. Hilditch CA, Brinjikji W, Schaafsma J, et al. Flow-diverter stents for internal carotid artery reconstruction following spontaneous dissection: a technical report. *Clin Neuroradiol*. 2019;29(4):707-715.
117. Ogawa A, Mori E, Minematsu K, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. *Stroke*. 2007;38(10):2633-2639.
118. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11-20.
119. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019-1030.
120. Molina CA, Chamorro A, Rovira A, et al. REVASCAT: a randomized trial of revascularization with SOLITAIRE FR device vs. best medical therapy in the treatment of acute stroke due to anterior circulation large vessel occlusion presenting within eight-hours of symptom onset. *Int J Stroke*. 2015;10(4):619-626.
121. McDowell MM, Ducruet AF. Time is brain: a critical analysis of the EXTEND-IA and ESCAPE trials. *World Neurosurg*. 2015;83(6):949-951.
122. Higashida R, Furlan A, Roberts H, et al. Trial design and reporting standards for intraarterial cerebral thrombolysis for acute ischemic stroke. *J Vasc Interv Radiol*. 2003;14(9 Pt 2):S493-S494.
123. Sivan-Hoffmann R, Gory B, Armoiry X, et al. Stent-retriever thrombectomy for acute anterior ischemic stroke due to proximal intracranial anterior circulation occlusion: a systematic review and meta-analysis. *Eur Radiol*. 2017;27(1):247-254.
124. Chen J, Wan T-F, Xu T-C, Chang G-C, Chen H-S, Liu L. Direct endovascular thrombectomy or with prior intravenous thrombolysis for acute ischemic stroke: a meta-analysis. *Front Neurol*. 2021;12:752698.
125. Abou-Chebl A. Endovascular treatment of acute ischemic stroke may be safely performed with no time window limit in appropriately selected patients. *Stroke*. 2010;41(9):1996-2000.
126. Jovin TG, Liebeskind DS, Gupta R, et al. Imaging-based endovascular therapy for acute ischemic stroke due to proximal intracranial anterior circulation occlusion treated beyond 8 hours from time last seen well: retrospective multicenter analysis of 237 consecutive patients. *Stroke*. 2011;42(8):2206-2211.
127. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for health-care professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49(3):e46-e110.
128. Abou-Chebl A, Lin R, Hussain MS, et al. Conscious sedation versus general anesthesia during endovascular therapy for acute anterior circulation stroke: preliminary results from a retrospective, multicenter study. *Stroke*. 2010;41(6):1175-1179.
129. Davis MJ, Menon BK, Baghirzadeh LB, et al. Anesthetic management and outcome in patients during endovascular therapy for acute stroke. *Anesthesiology*. 2012;116(2):396-405.
130. Gupta R. Local is better than general anesthesia during endovascular acute stroke interventions. *Stroke*. 2010;41(11):2718-2719.
131. Molina CA, Selim MH. General or local anesthesia during endovascular procedures: sailing quiet in the darkness or fast under a daylight storm. *Stroke*. 2010;41(11):2720-2721.
132. Abou-Chebl A, Yeatts SD, Yan B, et al. Impact of general anesthesia on safety and outcomes in the endovascular arm of Interventional Management of Stroke (IMS) III trial. *Stroke*. 2015;46(8):2142-2148.
133. Brinjikji W, Murad MH, Rabinstein AA, Cloft HJ, Lanzino G, Kallmes DF. Conscious sedation versus general anesthesia during endovascular acute ischemic stroke treatment: a systematic review and meta-analysis. *AJNR Am J Neuroradiol*. 2015;36(3):525-529.
134. Brinjikji W, Pasternak J, Murad MH, et al. Anesthesia-related outcomes for endovascular stroke revascularization: a systematic review and meta-analysis. *Stroke*. 2017;48(10):2784-2791.
135. Goldhoorn RB, Bernsen MLE, Hofmeijer J, et al. Anesthetic management during endovascular treatment of acute ischemic stroke in the MR CLEAN Registry. *Neurology*. 2020;94(1):e97-e106.
136. Simonsen CZ, Yoo AJ, Sørensen LH, et al. Effect of general anesthesia and conscious sedation during endovascular therapy on infarct growth and clinical outcomes in acute ischemic stroke: a randomized clinical trial. *JAMA Neurol*. 2018;75(4):470-477.
137. Ren C, Xu G, Liu Y, Liu G, Wang J, Gao J. Effect of conscious sedation vs. general anesthesia on outcomes in patients undergoing mechanical thrombectomy for acute ischemic stroke: a prospective randomized clinical trial. *Front Neurol*. 2020;11:170.
138. Schönenberger S, Uhlmann L, Hacke W, et al. Effect of conscious sedation vs general anesthesia on early neurological improvement among patients with ischemic stroke undergoing endovascular thrombectomy: a randomized clinical trial. *JAMA*. 2016;316(19):1986-1996.
139. Sacco RL, Kargman DE, Zamanillo MC. Race-ethnic differences in stroke risk factors among hospitalized patients with cerebral infarction: the Northern Manhattan Stroke Study. *Neurology*. 1995;45(4):659-663.
140. Thijs VN, Albers GW. Symptomatic intracranial atherosclerosis: outcome of patients who fail antithrombotic therapy. *Neurology*. 2000;55(4):490-497.
141. Wityk RJ, Lehman D, Klag M, Coresh J, Ahn H, Litt B. Race and sex differences in the distribution of cerebral atherosclerosis. *Stroke*. 1996;27(11):1974-1980.
142. Yadav JS, Abou-Chebl A. Intracranial angioplasty and stenting. *J Interv Cardiol*. 2009;22(1):9-15.
143. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med*. 2005;352(13):1305-1316.
144. The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. *N Engl J Med*. 1985;313(19):1191-1200.
145. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med*. 2011;365(11):993-1003.
146. Abou-Chebl A, Steinmetz H. Critique of "stenting versus aggressive medical therapy for intracranial arterial stenosis" by Chimowitz et al in the *New England Journal of Medicine*. *Stroke*. 2012;43(2):616-620.
147. Abou-Chebl A, Krieger DW, Bajzer CT, Yadav JS. Intracranial angioplasty and stenting in the awake patient. *J Neuroimaging*. 2006;16(3):216-223.
148. Liebeskind DS, Cotsonis GA, Saver JL, et al. Collaterals dramatically alter stroke risk in intracranial atherosclerosis. *Ann Neurol*. 2011;69(6):963-974.
149. Lau AY, Wong EH, Wong A, Mok FC, Leung TW, Wong KS. Significance of good collateral compensation in symptomatic intracranial atherosclerosis. *Cerebrovasc Dis*. 2012;33(6):517-524.
150. US Food and Drug Administration. Available at: <https://www.fda.gov/medical-devices/medical-device-safety/use-stryker-wingspan-stent-system-outside-approved-indications-leads-increased-risk-stroke-or-death>.
151. Gupta R, Schumacher HC, Mangla S, et al. Urgent endovascular revascularization for symptomatic intracranial atherosclerotic stenosis. *Neurology*. 2003;61(12):1729-1735.
152. Connors JR III, Wojak JC. Percutaneous transluminal angioplasty for intracranial atherosclerotic lesions: evolution of technique and short-term results. *J Neurosurg*. 1999;91(3):415-423.
153. Jiang W-J, Cheng-Ching E, Abou-Chebl A, et al. Multicenter analysis of stenting in symptomatic intracranial atherosclerosis. *Neurosurgery*. 2012;70(1):25-30.
154. Hinton RC, Mohr JP, Ackerman RH, Adair LB, Fisher CM. Symptomatic middle cerebral artery stenosis. *Ann Neurol*. 1979;5(2):152-157.
155. Ovbiagele B, Cruz-Flores S, Lynn MJ, Chimowitz MI. Early stroke risk after transient ischemic attack among individuals with symptomatic intracranial artery stenosis. *Arch Neurol*. 2008;65(6):733-737.
156. Adams HP Jr, Gross CE. Embolism distal to stenosis of the middle cerebral artery. *Stroke*. 1981;12(2):228-229.
157. Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. *Neurology*. 1989;39(9):1246-1250.
158. Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. *Arch Neurol*. 1998;55(11):1475-1482.
159. Thomson RM, Anderson DC. Aspirin and clopidogrel for prevention of ischemic stroke. *Curr Neurol Neurosci Rep*. 2013;13(2):327.
160. Jiang W-J, Yu W, Du B, Wong EH, Gao F. Wingspan experience at Beijing Tiantan Hospital: new insights into the mechanisms of procedural complication from viewing intraoperative transient ischemic attacks during awake stenting for vertebrobasilar stenosis. *J Neurointerv Surg*. 2010;2(2):99-103.
161. SSYLIVA Study Investigators. Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLIVA): study results. *Stroke*. 2004;35(6):1388-1392.

162. Bose A, Hartmann M, Henkes H, et al. A novel, self-expanding, nitinol stent in medically refractory intracranial atherosclerotic stenoses: the Wingspan study. *Stroke*. 2007;38(5):1531-1537.
163. Zaidat OO, Fitzsimmons B-F, Woodward BK, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. *JAMA*. 2015;313(12):1240-1248.
164. Abou-Chebl A, Bashir Q, Yadav JS. Drug-eluting stents for the treatment of intracranial atherosclerosis: initial experience and midterm angiographic follow-up. *Stroke*. 2005;36(12):e165-e168.
165. Mazighi M, Yadav JS, Abou-Chebl A. Durability of endovascular therapy for symptomatic intracranial atherosclerosis. *Stroke*. 2008;39(6):1766-1769.
166. Lee TH, Choi CH, Park K-P, et al. Techniques for intracranial stent navigation in patients with tortuous vessels. *AJNR Am J Neuroradiol*. 2005;26(6):1375-1380.
167. Reigel MM, Hollier LH, Sundt TM Jr, Piepgras DG, Sharbrough FW, Cherry KJ. Cerebral hyperperfusion syndrome: a cause of neurologic dysfunction after carotid endarterectomy. *J Vasc Surg*. 1987;5(4):628-634.
168. Meyers PM, Higashida RT, Phatouros CC, et al. Cerebral hyperperfusion syndrome after percutaneous transluminal stenting of the craniocervical arteries. *Neurosurgery*. 2000;47(2):335-343; discussion 343-345.
169. Abou-Chebl A, Yadav JS, Reginelli JP, Bajzer C, Bhatt D, Krieger DW. Intracranial hemorrhage and hyperperfusion syndrome following carotid artery stenting: risk factors, prevention, and treatment. *J Am Coll Cardiol*. 2004;43(9):1596-1601.
170. Khatri R, Ansar M, Sultan F, et al. Requirements for emergent neurosurgical procedures among patients undergoing neuroendovascular procedures in contemporary practice. *AJNR Am J Neuroradiol*. 2012;33(3):465-468.
171. Abou-Chebl A, Reginelli J, Bajzer CT, Yadav JS. Intensive treatment of hypertension decreases the risk of hyperperfusion and intracerebral hemorrhage following carotid artery stenting. *Catheter Cardiovasc Interv*. 2007;69(5):690-696.
172. Diener H-C, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364(9431):331-337.
173. Bhatt DL, Flather MD, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol*. 2007;49(19):1982-1988.
174. Rasmussen PA, Perl J II, Barr JD, et al. Stent-assisted angioplasty of intracranial vertebrobasilar atherosclerosis: an initial experience. *J Neurosurg*. 2000;92(5):771-778.
175. Alazzaz A, Thornton J, Aletich VA, Debrun GM, Ausman JJ, Charbel F. Intracranial percutaneous transluminal angioplasty for arteriosclerotic stenosis. *Arch Neurol*. 2000;57(11):1625-1630.
176. Abou-Chebl A, Krieger DW, Bajzer CT, Yadav JS. Intracranial angioplasty and stenting in the awake patient. *J Neuroimaging*. 2006;16(3):216-223.
177. Weber W, Mayer TE, Henkes H, et al. Stent-angioplasty of intracranial vertebral and basilar artery stenoses in symptomatic patients. *Eur J Radiol*. 2005;55(2):231-236.
178. Kim DJ, Lee BH, Kim DI, Shim WH, Jeon P, Lee TH. Stent-assisted angioplasty of symptomatic intracranial vertebrobasilar artery stenosis: feasibility and follow-up results. *AJNR Am J Neuroradiol*. 2005;26(6):1381-1388.
179. Higashida RT, Meyers PM, Connors JJ III, et al. Intracranial angioplasty & stenting for cerebral atherosclerosis: a position statement of the American Society of Interventional and Therapeutic Neuroradiology, Society of Interventional Radiology, and the American Society of Neuroradiology. *AJNR Am J Neuroradiol*. 2005;26(9):2323-2327.
180. Jiang W-J, Wang Y-J, Du B, et al. Stenting of symptomatic M1 stenosis of middle cerebral artery: an initial experience of 40 patients. *Stroke*. 2004;35(6):1375-1380.
181. Lee JH, Kwon SU, Lee JH, Suh DC, Kim JS. Percutaneous transluminal angioplasty for symptomatic middle cerebral artery stenosis: long-term follow-up. *Cerebrovasc Dis*. 2003;15(1-2):90-97.
182. Marks MP, Wojak JC, Al-Ali F, et al. Angioplasty for symptomatic intracranial stenosis: clinical outcome. *Stroke*. 2006;37(4):1016-1020.
183. Mori T, Kazita K, Chokyu K, Mima T, Mori K. Short-term arteriographic and clinical outcome after cerebral angioplasty and stenting for intracranial vertebrobasilar and carotid atherosclerotic occlusive disease. *AJNR Am J Neuroradiol*. 2000;21(2):249-254.
184. Lylyk P, Cohen JE, Ceratto R, Ferrario A, Miranda C. Angioplasty and stent placement in intracranial atherosclerotic stenoses and dissections. *AJNR Am J Neuroradiol*. 2002;23(3):430-436.
185. Gupta R, Al-Ali F, Thomas AJ, et al. Safety, feasibility, and short-term follow-up of drug-eluting stent placement in the intracranial and extracranial circulation. *Stroke*. 2006;37(10):2562-2566.
186. Abou-Chebl A. Intracranial stenting with Wingspan: still awaiting a safe landing. *Stroke*. 2011;42(7):1809-1811.
187. Alexander MJ, Zauner A, Chaloupka JC, et al. WEAVE trial: final results in 152 on-label patients. *Stroke*. 2019;50(4):889-894.
188. Alexander MJ, Zauner A, Gupta R, et al. The WOVEN trial: Wingspan one-year vascular events and neurologic outcomes. *J Neurointerv Surg*. 2021;13(4):307-310.



26

Interventional Management Of Lower Extremity Deep Vein Thrombosis And Pulmonary Embolism

VIKRAM RAJPUROHIT, MD, AKHILESH K. SISTA, MD, SURESH VEDANTHAM, MD

INTRODUCTION, 479

LOWER EXTREMITY DEEP VEIN THROMBOSIS, 479

ACUTE DEEP VEIN THROMBOSIS, 479

Epidemiology and Pulmonary Embolus Prevention, 479

Inferior Vena Cava Filters, 479

The Postthrombotic Syndrome, 480

Preventing the Postthrombotic Syndrome:

Beyond Anticoagulation, 481

Endovascular Thrombus Removal

Techniques, 481

Patient Selection, 483

Outcomes and Data, 483

CHRONIC DEEP VEIN THROMBOSIS, 484

Patient Workup, 484

Noninterventional Management of Postthrombotic Syndrome, 484

Endovascular Intervention in the Setting of Established Postthrombotic Syndrome, 484

Interventional Techniques to Recanalize

Postthrombotic Deep Veins, 485

Complications and Outcomes, 487

ACUTE PULMONARY EMBOLISM, 488

EPIDEMIOLOGY AND CLASSIFICATION, 488

TREATMENT ESCALATION FOR MASSIVE PULMONARY EMBOLISM, 488

TREATMENT ESCALATION FOR SUBMASSIVE PULMONARY EMBOLISM, 489

PATIENT FOLLOW-UP, 491

INTRODUCTION

Venous thromboembolic (VTE) disease, consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE), is morbid, expensive, and potentially fatal. It ranks as the third most common cardiovascular disease and consumes significant health care dollars.¹ Over the past several decades, the management of DVT and PE for many patients has been altered by the introduction of catheter-based therapies. Considerable data have been generated with these techniques during this time, although randomized trials are few. This chapter is divided into two sections, one discussing lower extremity DVT and the second describing the interventional management of PE. The DVT section reviews epidemiology, medical management, the postthrombotic syndrome (PTS) and its prevention, and both the conservative and interventional management of established PTS. Section 2 discusses the epidemiology, categorization, and escalation options for acute PE, with a focus on catheter-based techniques.

LOWER EXTREMITY DEEP VEIN THROMBOSIS

ACUTE DEEP VEIN THROMBOSIS

Epidemiology and Pulmonary Embolus Prevention

It is estimated that 350,000 to 600,000 acute symptomatic DVTs are diagnosed per year in the United States, out of which up to 250,000 are a new diagnosis in the lower

extremity. Given the 100,000 to 180,000 individuals who die of PE every year,¹ the treatment for DVT has traditionally focused on the prevention of PE through anticoagulation.² Historically, the majority of patients were initiated on a parenteral regimen as a bridge to an oral vitamin K antagonist (warfarin). Now, because of greater convenience, equivalent efficacy, and equal or better safety compared with warfarin, most patients are immediately started on a direct oral anticoagulants regimen.³ The duration of therapy is a minimum of 3 months but is otherwise based on multiple factors, the most important being the presence or absence of reversible provoking factors.

Inferior Vena Cava Filters

When anticoagulation is contraindicated or fails, inferior vena cava (IVC) filters can be inserted to prevent large thrombi from traveling to the lungs.² Filters may also be placed in the setting of a hemodynamically significant pulmonary embolus in a patient with limited cardiopulmonary reserve who would poorly tolerate additional emboli. However, multiple studies show no mortality benefit gained by routinely placing IVC filters as primary prophylaxis even in high-risk groups (e.g., trauma patients and patients with history of VTE who will be immobilized after major surgery for a prolonged period).⁴ Additionally, although IVC filters are effective at preventing PE, they may be associated with a number of complications, including filter hook or strut endothelialization, IVC wall perforation, component fracture and embolization, and caval thrombosis and occlusion.⁵

The PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) study from the late 1990s indicated that in patients with DVT who can be anticoagulated, permanent filters reduce the rate of symptomatic PE but increase the rate of symptomatic recurrent DVT, resulting in similar rates of symptomatic VTE to patients not receiving permanent IVC filters.⁶ Subsequently, the PREPIC-2 study in 2015 sought to evaluate the effectiveness of retrievable IVC filter placement in patients with acute PE at high risk for recurrence while on anticoagulation.⁷ However, despite focusing on a high-risk subgroup, the study showed no significant difference in symptomatic PE or mortality rates at 3 or 6 months.⁷ Thus, insertion of a filter should be performed only after a thorough evaluation of the short- and long-term risks and benefits. Moreover, when IVC filtration is no longer indicated, every effort should be made to remove the filter if safe to do so. Of note, the recently completed single-arm, multicenter prospective predicting the safety and effectiveness of inferior vena cava filters (PRESERVE) registry has collected data on outcomes in recipients of four commercially available temporary and permanent filters in the current market.⁸

Filter insertion can be performed via the internal jugular vein, common femoral vein, or arm vein (brachial, basilic, or cephalic) if the delivery sheath is low profile (Video 26.1). Especially in the absence of prior cross-sectional imaging, venography before insertion provides some valuable information. The size of the cava, position of the renal veins, presence of caval thrombus, caval duplication, and variant anatomy such as a circumaortic renal vein can all be detected. If possible, venography should be performed from the left common iliac vein because a duplicated cava can be detected most commonly from this position. Megacava is defined as a diameter greater than 28 mm; this finding is rare, and it is important to rule out a flattened cava by performing cavography at multiple obliquities. Most retrievable filters are indicated for IVC diameters up to 30 mm. However, if a larger IVC caliber is found, only filters capable of filling the entire diameter, such as a Bird's nest (Cook Medical) filter, should be deployed. If standard caval anatomy and size are present, the filter should be deployed inferior to the renal vein insertions to avoid trapped clot from propagating into the renal veins. In the event of caval duplication, two filters may be necessary (Figure 26.1). A circumaortic renal vein may require a suprarenal filter, given that it can act as a bypass circuit if the filter is inserted below its more cranial insertion. Postdeployment venography ensures proper positioning and may be useful for later retrieval.

As mentioned previously, given the later complications of IVC filters, the need for filtration should be reassessed at periodic time points after insertion if a retrievable filter was used; the optimal time frame for removal is within 4 to 6 weeks of placement. With time, filters can become embedded in the wall of the cava and more difficult to extract. At the time of retrieval, venography should be performed to exclude significant clot within the filter, which may preclude retrieval. A common feature of currently available retrievable filters is a “hook” at the top or bottom that can be engaged with a snare. The venous access site (femoral versus jugular) depends on filter design; however, most filters have the hook at the cranial aspect, necessitating a jugular approach. When the snare grasps the hook,

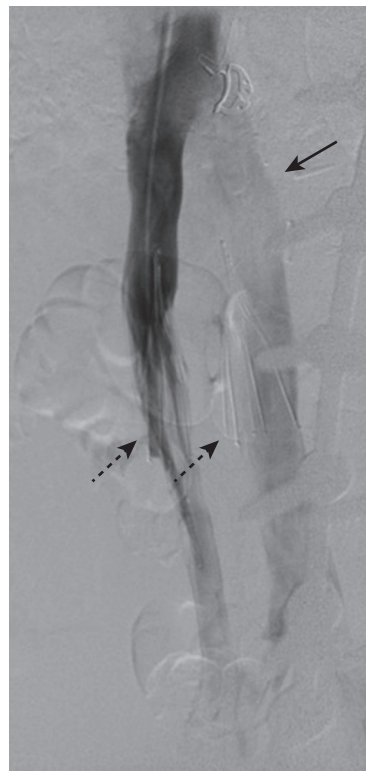


FIGURE 26.1 Inferior vena cavagram demonstrating a duplicated inferior vena cava (IVC) (solid arrow). Note the subtracted IVC filters (dashed arrows) in both the main and duplicated IVC.

an appropriately sized sheath (typically between 10 and 12 Fr) can be advanced over the filter to collapse it, and the filter is then pulled through the sheath out of the body (Video 26.2). Complex filter retrieval techniques when faced with embedded filters include the use of forceps or laser sheaths via large-bore access. Recently, the Sentry bioconvertible filter gained US Food and Drug Administration (FDA) 510k clearance for use as an alternative to retrievable filters in patients with VTE and a contraindication to anticoagulation.⁹ The filter is designed to bioconvert 60 days after implantation, obviating the need for removal. The Sentry trial, a multicenter, nonrandomized, single-arm study, demonstrated safety with efficacy outcomes comparable to those seen in previous retrievable filter studies.¹⁰

The Postthrombotic Syndrome

Despite the use of anticoagulation, about 40% of individuals with an acute symptomatic DVT experience some version of the PTS. PTS is a constellation of chronic symptoms and signs in the affected limb that includes pain, swelling, aching, paresthesias, fatigue, and heaviness that typically worsen as the day progresses and in the standing position. Severe manifestations include stasis dermatitis, venous claudication, and ulceration (Figure 26.2). PTS has been shown to adversely affect quality of life and self-perception, and the individual and societal costs (both direct medical and indirect loss of work) are high.¹¹⁻¹⁴ Thus, strategies that can prevent or reduce the severity of PTS need to be examined.

The development of PTS after a proximal DVT is thought to be secondary to a combination of obstruction and valvular



FIGURE 26.2 Severe postthrombotic syndrome with edema, hyperpigmentation, and healed ulcers.

damage. Although incompletely understood, the pathogenesis is related to an inflammatory leukocytic infiltration and cytokine release in response to acute thrombus that ultimately results in clot organization and wall thickening in the event of incomplete thrombus clearance.¹⁵⁻¹⁸ The narrowed lumen causes outflow obstruction, and in combination with damaged valves, results in venous hypertension and dilation of more peripheral uninvolved deep and superficial veins.¹⁹⁻²² Ultimately, the venous hypertension and reflux cause edema, calf pump dysfunction, tissue hypoxia, subcutaneous fibrosis, and ulceration.²³⁻²⁶

Several factors have been identified that place a patient at higher risk for developing PTS. These include recurrent ipsilateral DVT (2.6-fold increased risk),¹¹ subtherapeutic anticoagulation (2.5-fold increased risk),²⁷ and iliofemoral (iliac or common femoral vein) DVT (50% incidence of PTS despite use of anticoagulation).^{28,29} Minor risk factors include advanced age, obesity, and female gender.

Preventing the Postthrombotic Syndrome: Beyond Anticoagulation

Until recently, elastic compression stockings (ECSs) were considered standard of care in the prevention of PTS, given two randomized single-center studies that demonstrated a reduction in PTS with their daily use.^{30,31} However, the much larger placebo-controlled, double-blind, randomized controlled multicenter compression stockings to prevent post-thrombotic syndrome (SOX) trial demonstrated an equally high rate of PTS in the ECS group as the “sham” stocking group.³² Thus, the best evidence suggests that ECS therapy does not prevent PTS. However, a case-by-case approach may be appropriate to control PTS symptoms during long-term follow-up; if ECSs provide symptomatic relief and there are no contraindications (e.g., peripheral arterial disease, skin hypersensitivity), the patient may certainly use them.

Given the high incidence of PTS after a symptomatic proximal DVT despite therapeutic anticoagulation, thromboreductive strategies, ranging from systemic thrombolysis

to surgical embolectomy to catheter-directed techniques, have been trialed. These more aggressive strategies are predicated on the “open-vein” theory, which maintains that restoring patency to a thrombosed vein makes that vein less susceptible to rethrombosis, reflux, and the pathophysiologic process leading to PTS. There is significant evidence to support the open-vein theory. Prandoni et al.²² noted higher 2-year rates of PTS in patients who had residual thrombus at 6 months. Hull et al.³³ found a strong correlation between the amount of residual thrombus and recurrent VTE, which, as stated earlier, correlates with higher rates of PTS. Taking the lessons of small studies examining systemic thrombolysis and surgical embolectomy, aggressive thrombus clearance resulted in lower rates of PTS (albeit at the cost of higher morbidity and bleeding rates).³⁴⁻³⁶

Catheter-directed therapy has the potential to match or improve the efficacy of systemic thrombolysis or surgical embolectomy with less morbidity and bleeding. This approach allows for intrathrombus injection or infusion of fibrinolytic drug to allow for greater clot penetration. Studies have demonstrated that nonocclusive thrombi are much more likely to be lysed than occlusive thrombi when systemic thrombolytic drugs are administered,³⁷ implying that when the lytic drug is capable of reaching thrombus (as it does with catheter-directed therapy), it has a greater likelihood of lysing it. However, despite no meaningful benefit between systemic and catheter-directed administration, guidelines continue to suggest the use of catheter-directed intrathrombus infusion over systemic infusion because of the possibly reduced risk of major bleeding with catheter-directed administration in patients with symptomatic proximal DVT.³⁸⁻⁴¹

Endovascular Thrombus Removal Techniques

Catheter-directed therapies have evolved considerably over the past 3 decades to minimize complications and maximize efficacy and patient comfort. Under the umbrella of endovascular thrombus removal are the following methods: catheter-directed thrombolysis (CDT), percutaneous mechanical thrombectomy (PMT), and pharmacomechanical catheter-directed thrombolysis (PCDT). The procedural details of these variant techniques and their results are discussed next.

Catheter-directed thrombolysis refers to the placement of a multi-sidehole infusion catheter into the thrombus with subsequent infusion of a lytic drug over a period of time. Access is gained most commonly into the popliteal vein under ultrasound guidance. After a guidewire and catheter traverse the clot, venography is performed to delineate thrombus extent. Next, an appropriately sized multi-sidehole infusion catheter is positioned within the clot, and an infusion of recombinant tissue plasminogen activator (rt-PA), reteplase, or tenecteplase is started. It should be noted that none of these drugs are FDA approved for the treatment of patients with DVT. Infusion on average lasts between 6 and 24 hours, after which the patient is brought back to the interventional suite for repeat venography. If an underlying obstructive lesion is identified in the deep pelvic veins, it can be stented to reduce the

incidence of early recurrent thrombosis and improve outflow and symptomatology.⁴²

In a multicenter registry conducted in the late 1990s, the major bleeding rate from CDT was found to be 11%.³⁹ Since then, limiting the hourly rt-PA dose, reducing the heparin to “subtherapeutic” levels (e.g., partial thromboplastin time 1.2–1.7 times control), and routinely using ultrasound guidance have reduced the major bleed rate to 2% to 4%.⁴³⁻⁴⁵ Ultrasound-assisted thrombolysis has been hypothesized to speed the time to lysis and improve lytic drug efficacy; however, the technology was ineffective in improving clot lysis or reducing PTS in two small randomized trials (one comparing against standard thrombolytic infusion, the other against anticoagulation alone).^{46,47}

Percutaneous mechanical thrombectomy refers to clot removal from the venous lumen with use of a catheter-based mechanical device. The rationale is that partial thrombus reduction with a mechanical device will create a flow

channel and increase the surface area for endogenous thrombolysis. Either through a 7- or 8-Fr catheter or using a specialized device, thrombus is aspirated from the obstructed vein. Results of legacy devices have been fairly disappointing without the addition of a thrombolytic agent, and clot manipulation carries the risk of embolism and valvular damage.⁴² Recently, large-bore catheters up to 24 Fr in size have been trialed for thromboaspiration, especially in patients with ilio caval occlusions and contraindications to thrombolysis. However, prospective studies are unavailable.

Pharmacomechanical catheter-directed thrombolysis (Figure 26.3) is a combination of the other two techniques that uses both mechanical methods and fibrinolytic drugs to achieve thrombus reduction. The mechanical portion macerates thrombus and promotes intrathrombus dispersion of the lytic drug, and the lytic component reduces the risk of embolism and results in more complete lysis. The

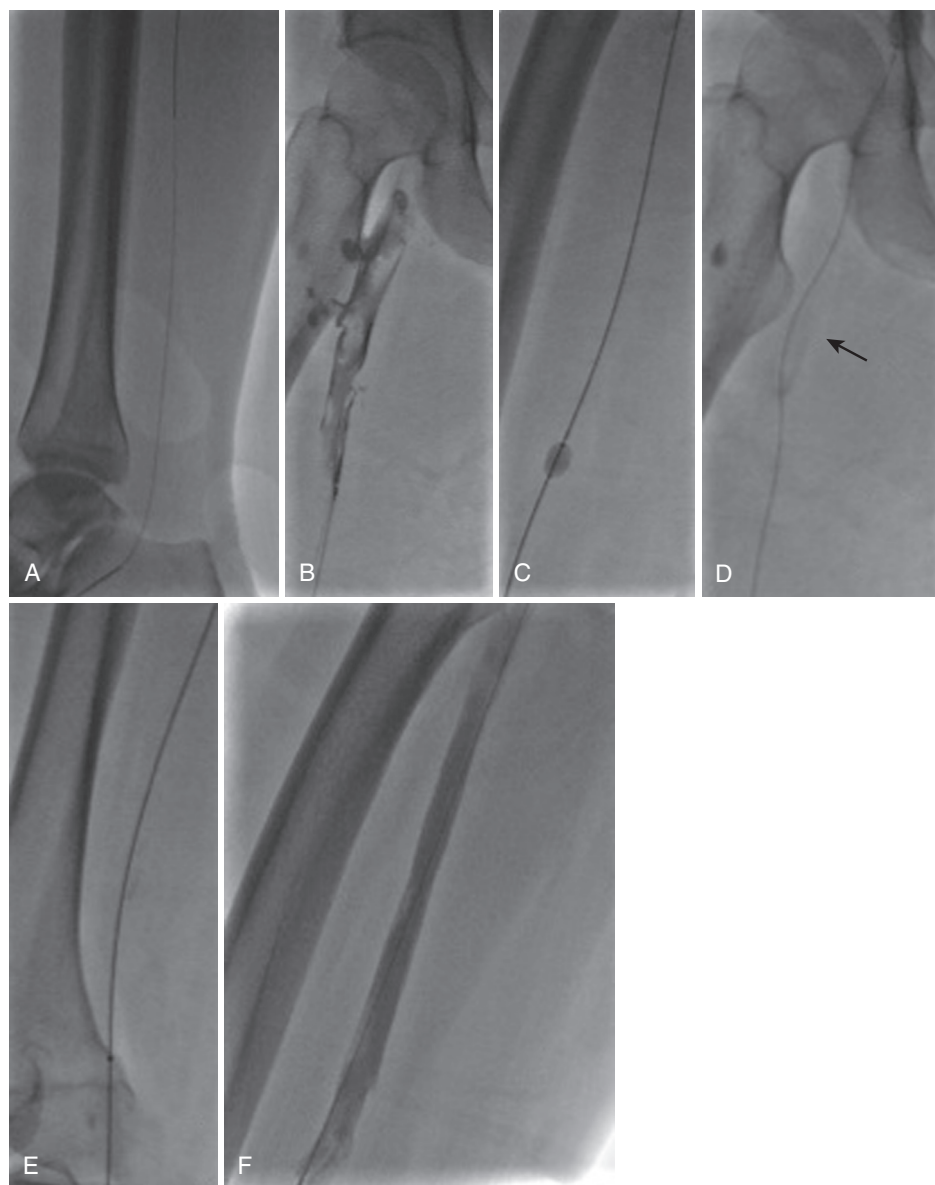


FIGURE 26.3 Pharmacomechanical catheter-directed thrombolysis. **A**, Posterior tibial vein access (performed under ultrasound guidance). **B**, Acute thrombus in the femoral vein extending into the common femoral vein. **C** and **D**, Trellis device infusing lytic and macerating thrombus with a sinusoidal wire (arrow) within the catheter between the proximal and distal (**D**) balloons. **E**, Placement of an infusion catheter across the thrombus. **F**, Venographic appearance after 20 hours of lytic infusion, demonstrating near 100% thrombus clearance.

TABLE 26.1 Patient Selection for Catheter-Based Treatment of Acute Lower Extremity Deep Vein Thrombosis

DVT PRESENTATION	BLEEDING RISK		
	LOW	MODERATE	HIGH
Proximal DVT with limb threat	Yes	Yes	Possibly, with surgical consultation
IVC thrombus	Yes	Yes	No
DVT symptom progression or thrombus progression on anticoagulation	Yes	Possibly	No
Iliofemoral DVT to prevent PTS	Usually yes	No	No

DVT, Deep vein thrombosis; IVC, inferior vena cava; PTS, postthrombotic syndrome.

addition of PMT to CDT has been shown to reduce the dose of lytic drug required and reduce infusion duration.⁴⁸ More recently, PCDT has evolved to include techniques that enable very rapid drug dispersion, often permitting single-session DVT treatment.

Patient Selection (Table 26.1)

The decision of whether to proceed with thrombolysis is based on a risk-benefit analysis that incorporates the severity of the patient's clinical presentation, the projected risk of bleeding, the duration of symptoms (i.e., likelihood that thrombus will lyse), and the patient's preferences. Acute limb threat and thrombus extension or worsening symptoms despite adequate anticoagulation have lower thresholds for intervention to minimize short-term mortality and morbidity. If none of these is present, the decision to lyse is normally based on the desire to lessen the severity of PTS and alleviate severe symptoms of the acute DVT, if present.⁴⁹ Thus, a younger patient with a reasonable life expectancy, a low likelihood of bleeding, and an acute iliofemoral DVT (which, as stated earlier, has the strongest association with more severe PTS) is most likely to be a good candidate for intervention. In contrast, patients with DVT limited to the femoropopliteal or calf veins do not benefit from thrombolytic therapy (Kearon et al.,⁵⁰ Acute venous thrombosis: thrombus removal with adjunctive catheter-directed thrombolysis [ATTRACT] study).

Outcomes and Data (Table 26.2)

Numerous small studies have been performed on outcomes associated with endovascular thrombus removal that suggest improved venous patency rates and long-term venous symptom outcomes. It should be noted that significant methodologic flaws exist for each, however, including small sample size, lack of randomization, single-center experience, and lack of objective measures of PTS. Comerota et al.⁵¹ conducted a multicenter registry and found improved rates of PTS and quality of life in the treated group. AbuRahma et al.⁵² performed a nonrandomized comparison of treated and untreated groups and found better 5-year symptoms and venous patency. Elsharawy et al.⁵³ conducted a single-center randomized trial that showed higher venous patency rates and less reflux in the catheter-treated group.

The first multi-center randomized controlled CaVenT study was completed in Norway and showed a 26% relative risk reduction in the 2-year occurrence of PTS in those who received CDT. However, quality of life was not impacted by

TABLE 26.2 Catheter-Directed Thrombolysis: Comparative Studies

REFERENCE	DESIGN	OUTCOME
Comerota et al. ⁵¹ (2000)	Multicenter registry	Reduction in PTS and improved physical functioning
AbuRahma et al. ⁵² (2001)	Prospective nonrandomized trial	Improved patency and freedom from symptoms
Elsharawy and Elzayat ⁵³ (2002)	Randomized single-center trial	Higher return to normal venous function
CaVenT ⁵⁴ (2012)	Multicenter randomized trial	Significant improvement in 2-y rate of PTS
ATTRACT ⁵⁵ (2017)	Multicenter randomized trial	No difference in incidence of PTS Reduced severity of PTS

ATTRACT, Acute venous thrombosis: thrombus removal with adjunctive catheter-directed thrombolysis; CaVenT, catheter-directed venous thrombolysis in acute iliofemoral vein thrombosis; PTS, postthrombotic syndrome.

the performance of CDT, and most PTS cases were mild. This study was limited by its modest sample size ($n = 209$) and only trialed multiday infusion CDT.⁵⁴

To clarify many of these uncertainties, the National Institutes of Health (NIH)-sponsored ATTRACT trial sought to definitively answer whether PCDT should be an adjunctive treatment of symptomatic proximal DVT to prevent PTS.⁵⁵ This landmark study ($n = 692$) found no significant difference in occurrence of PTS through 24 months between groups that received PCDT and those that did not.⁵⁶ Additionally, there was slight increase in major bleeding risk (1.7% vs 0.3%) in the PCDT group with no difference in rate of recurrent VTE or quality of life scores over 24 months.⁵⁶ Subgroup analysis of only those patients with iliofemoral DVT ($n = 391$) demonstrated no difference in the occurrence of PTS or recurrent VTE; however, PCDT did significantly decrease early leg symptoms at 10 and 30 days, reduce PTS severity, and decrease the proportion of patients with moderate or severe PTS (Villalta score >10) through 24 months.⁴ Patients with iliofemoral DVT who received PCDT did experience greater improvement in venous disease-specific quality of life over 24 months; this difference was most pronounced within the first 6 months. Conversely, in subgroup analysis of patients with only femoropopliteal DVT ($n = 300$), PCDT did not produce any clinical benefit. Cost-effectiveness analysis of PCDT in the ATTRACT trial additionally demonstrated an unfavorable incremental cost effectiveness ratio of \$222,041 per quality adjusted life year.⁵⁷ Finally, although PCDT reduced the extent of residual thrombus, it did not alter the occurrence of valvular reflux. Less thrombus burden in the common

femoral vein (CFV) was shown to be associated with less PTS, less moderate or severe PTS, and better quality of life⁵⁸; however, this did not apply to thrombus in femoral or popliteal veins.⁵⁹ In light of these analyses, PCDT is not an economically attractive or effective treatment option for patients with isolated femoropopliteal DVT; however, it is reasonable to consider for highly selected patients who have symptomatic iliofemoral DVT at low risk of bleeding who favor aggressive treatment.

CHRONIC DEEP VEIN THROMBOSIS

Chronic venous insufficiency is costly and morbid, with venous ulcers alone costing \$3 billion per year and resulting in the loss of 2 million working days per year.⁶⁰ Historical data suggest that PTS accounts for at least about 12% of chronic venous insufficiency cases.⁶¹ As alluded to in the previous section, incomplete thrombus clearance and organization result in endothelialized channels that partially recanalize the vein. The extent of this recanalization and collateral formation partly determines whether the patient will develop PTS. Most patients present with mild to moderate PTS, and a minority present with severe PTS or ulcer formation.

Patient Workup

Pertinent data to gather include a history of VTE, trauma, IVC filter placement, dialysis catheter placement, a family history of VTE, or malignancy. The duration and severity of symptoms should also be documented; a sudden exacerbation may represent an acute thrombotic episode. Using standardized assessments of venous disease (e.g., CEAP [Clinical-Etiology-Anatomy-Pathophysiology], Venous Clinical Severity Scale, Villalta Scale) establishes a baseline and enables longitudinal tracking of clinical progress (Table 26.3). A photograph of the affected limb(s) and calf and thigh circumferences can be added to the baseline assessment. Understanding the anatomic extent of the postthrombotic veins is essential for treatment planning; Doppler sonography can assess up to the peripheral external iliac vein, but routinely visualizing pelvic veins and the IVC commonly requires cross-sectional imaging (magnetic resonance venography or computed tomography; Figure 26.4) or venography with intravascular ultrasound.

Noninterventional Management of Postthrombotic Syndrome

Several measures can be taken to optimize a patient with existing PTS. First, the anticoagulation status should be assessed, and all efforts should be made to prevent rethrombosis, including prolonged anticoagulation if appropriate and safe. Compression stockings and similar devices may provide symptomatic relief.^{2,62,63} Weight loss, smoking cessation, and exercise⁶³ should be encouraged to minimize symptoms. Optimal wound care for those with venous ulcers includes inelastic compression, analgesics, antiinflammatories, lymphedema therapy, surgical debridement, and antibiotics if necessary.

TABLE 26.3 CEAP and Villalta Classifications

"C" or "Clinical" Definition of CEAP Classification
C0: No signs of venous disease
C1: Telangiectasias or reticular veins
C2: Varicosities
C3: Edema
C4a: Venous eczema or hyperpigmentation
C4b: Lipodermatosclerosis
C5: Healed ulcer
C6: Active ulcer
Villalta Scale ^a
Symptoms
• Cramps
• Itching
• Pins and needles
• Leg heaviness
• Pain
Signs
• Pretibial edema
• Skin induration
• Hyperpigmentation
• Venous ectasia
• Redness
• Pain during calf compression
• Ulceration

^aEach symptom or sign is graded from 0 to 3, with 0 = none and 3 = severe. Score >5 = PTS. Ulceration = automatic severe PTS.
CEAP, Clinical-Etiology-Anatomy-Pathophysiology; PTS, postthrombotic syndrome.

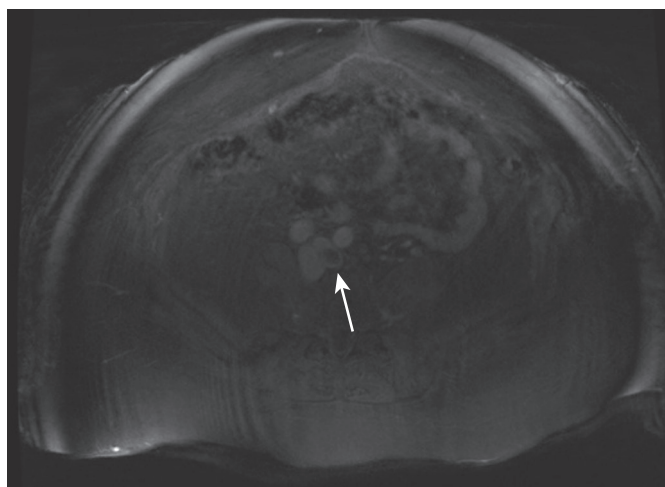


FIGURE 26.4 Magnetic resonance imaging of the pelvis demonstrating a central thrombus (arrow) in the left common iliac vein.

Endovascular Intervention in the Setting of Established Postthrombotic Syndrome

Before endovascular recanalization techniques, surgical bypass was the primary means of improving flow in patients with severe clinical manifestations from ilio caval venous obstruction. Now it is reserved for those who fail endovascular treatment.⁶⁴ Patients who are being considered for endovascular recanalization should obtain a full set of laboratory studies (complete blood count, international normalized ratio, basic metabolic profile). Recanalization should be performed with the patient fully anticoagulated to avoid thrombosis during and after the procedure. Because of the stimulating nature and length of the procedure, the majority of recanalizations may require the use of

general anesthesia. If a patient is not on anticoagulation, he or she should be a candidate for it given that some length of anticoagulation in a postthrombotic patient is necessary after the placement of endovenous stents.

Interventional Techniques to Recanalize Postthrombotic Deep Veins

As mentioned earlier, knowing the extent of thrombosis or stenosis and the cause is essential for interventional planning and goals. Three common scenarios will be discussed: IVC and iliac occlusion secondary to an embedded IVC filter, iliofemoral chronic thrombosis, and femoropopliteal chronic thrombosis.

Caval stenosis or occlusion secondary to an embedded IVC filter occurs at a rate of approximately 1% to 2%.⁶ The mechanism is unclear but is thought to be a combination of organized thrombus and a fibrotic response to the

metallic elements of the filter.⁶⁵ It is also unclear how long it takes this process to develop and why it occurs in some individuals but not in most. Filter removal, if it can be performed safely, should be attempted before recanalization. Because the filter is commonly embedded, extraction may require advanced endovascular techniques, including the loop-snare technique, excimer-laser assisted removal, and grasping forceps.^{66,67} If the hook cannot be grasped, the loop-snare technique may allow the interventionalist to center the filter and sheath over it or use forceps once centered. In cases of wall adhered filters, laser assistance may be helpful to lyse fibrous tissue between the filter metal and the cava. It is important to note that although these techniques are generally safe, complications including caval perforation and fragment embolization have been encountered.⁶⁸ After the filter has been removed, wire access across the stenosis or occlusion is the next essential step (Figure 26.5). Angioplasty is then performed

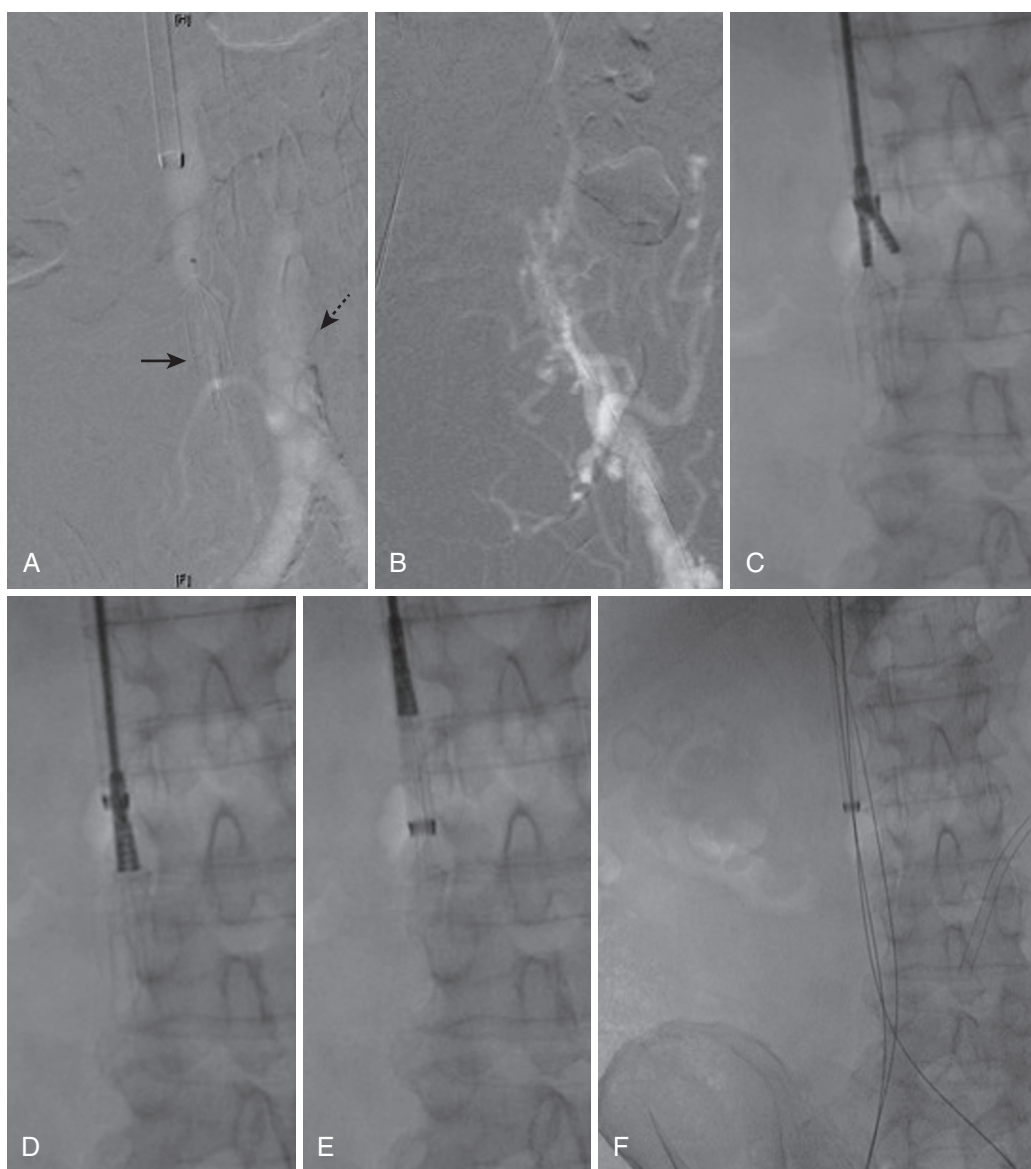


FIGURE 26.5 **A**, Inferior vena cavagram with carbon dioxide as a contrast agent (because of renal insufficiency) showing no flow below a chronically embedded inferior vena cava (IVC) filter (*solid arrow*). Incidentally, a small arteriovenous fistula outlines the aorta (*dashed arrow*), likely seen because of the low viscosity of carbon dioxide. **B**, Left common iliac venography shows no flow into the IVC with marked collateralization. **C–E**, Retrieval of the chronically embedded filter using forceps. **F**, Successful wire placement across obstructed iliocaval segments.

Continued

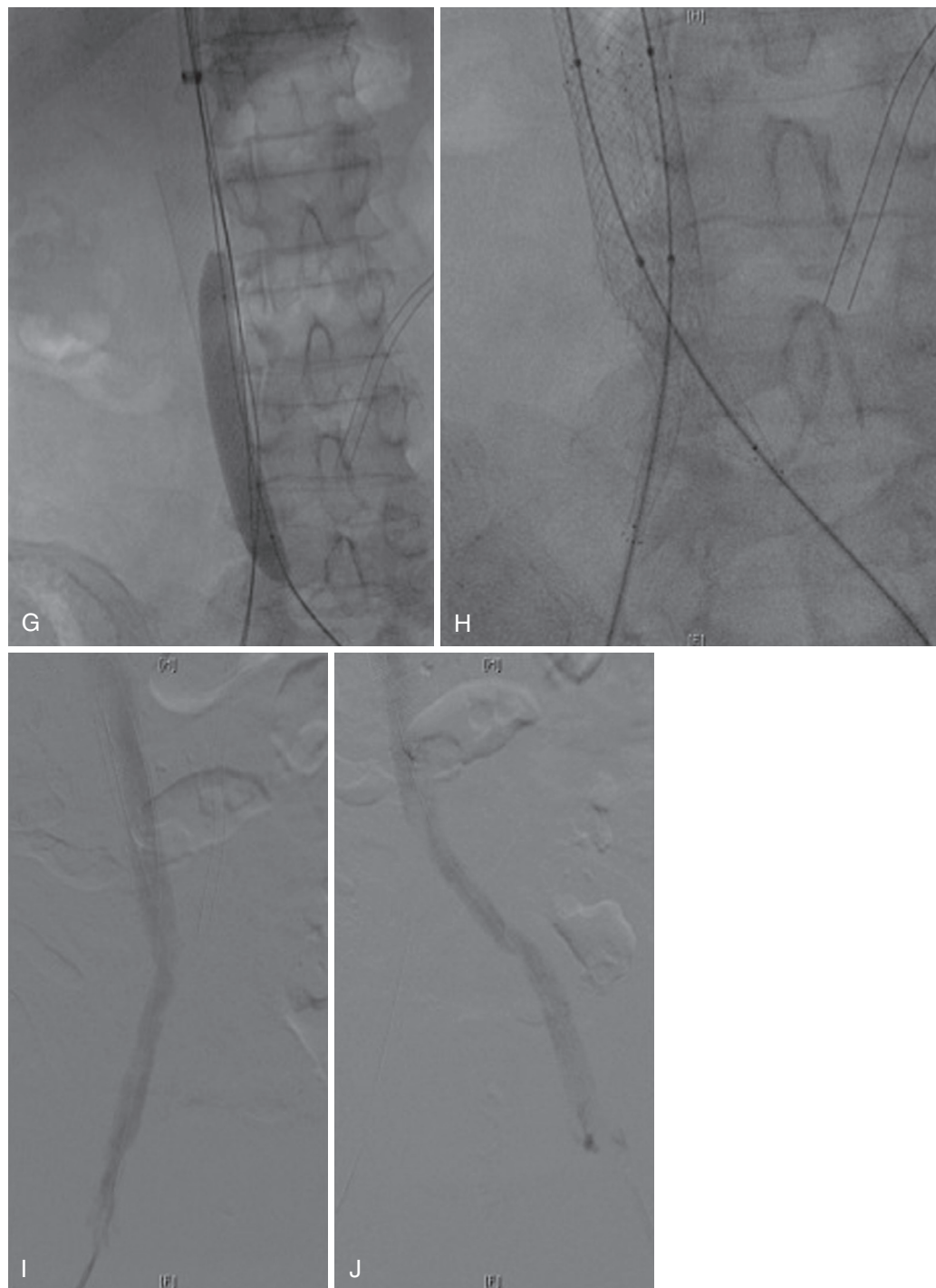


FIGURE 26.5, cont'd **G**, Intrastent angioplasty after deployment of a self-expanding IVC stent. **H**, Deployment of bilateral kissing iliac stents. **I** and **J**, Completion venography with dilute contrast demonstrating brisk flow through stented iliac veins and IVC with resolution of collaterals.

to facilitate the introduction of stent catheters, if necessary, especially in very tight stenoses or long-standing occlusions. Typical self-expanding caval stent sizes range in diameter from 20 to 24 mm. Balloon-expandable stents are reserved for particularly recalcitrant lesions. Frequently, the chronic thrombosis extends into both iliac veins, necessitating “kissing” iliac stents into the IVC stent. Common iliac stent sizes range from 12 to 18 mm; self-expanding nitinol or stainless steel stents are most commonly used.

A number of dedicated venous stents have emerged on the market, though they have yet to demonstrate improved patency or clinical outcomes compared with older stents.

Iliofemoral occlusions from a prior DVT require a popliteal puncture or jugular access because the thrombosis extends to the common femoral vein and the femoral vein as well. These iliofemoral occlusions may have been the result of a May-Thurner lesion or one of its variants

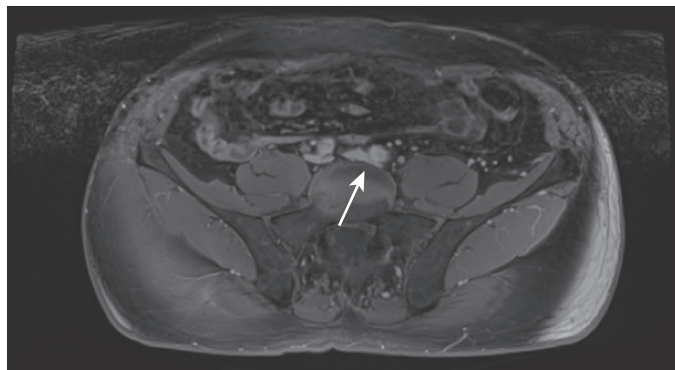


FIGURE 26.6 Magnetic resonance imaging of the pelvis demonstrating compression of the left common iliac vein (arrow) between the left common iliac artery and vertebral body (May-Thurner variant).

(Figure 26.6). Classic May-Thurner syndrome results from compression of the left common iliac vein by the pulsating right common iliac artery anteriorly and the vertebral body posteriorly causing intraluminal webs and fibrous bridging leading to thrombosis and venous hypertension. Although up to 25% to 30% of the population have been shown to have this feature anatomically, it is unclear why some develop symptoms and most are asymptomatic.⁶⁹ Regardless, treating an iliofemoral occlusion may require stenting up to and possibly into the IVC to open the May-Thurner compression. Routine puncture of the femoral vein along the thigh should be avoided, given the difficulty compressing it against a bony structure and the theoretically higher potential for a postoperative hematoma. If access to the CFV is needed, puncture should be obtained either via the popliteal vein or jugular vein. Obtaining wire access across the occluded iliofemoral segment is often the most challenging part of the case and is most frequently accomplished with the combination of a hydrophilic wire and strong support catheter. Occasionally, more vigorous methods are necessary, including sharp recanalization techniques such as the back end of wires (Figure 26.7).⁷⁰ After wire access is obtained, stenting is performed as discussed earlier. The stents need to extend to a segment of open flow, although routine stenting of the femoral vein should be avoided because of historically low patency rates. If the femoral vein is occluded, extending the stents into the profunda femoral vein may be necessary to provide adequate inflow.

Treating patients with chronic femoropopliteal disease in the absence of iliac obstruction is more controversial. Although thought to confer a much lower risk of PTS,¹⁰ chronic femoropopliteal disease can result in bothersome symptoms, especially to active individuals. For these patients, attempted recanalization using angioplasty can be attempted, but the long-term results are unknown, and given the significant recoil of a fibrotic postthrombotic vein, the valvular damage it has already sustained, and the possibility of rethrombosis, more data need to be gathered before routine use of this technique can be recommended.

Most individuals will need at least a short duration of anticoagulation after a recanalization, most commonly for 3 months. Antiplatelet agents, including aspirin and



FIGURE 26.7 Sharp recanalization through a chronically occluded stent (dashed arrow) with the back end of a stiff wire (solid arrow).

clopidogrel, can be added to aid in stent patency. The optimal duration of therapy or regimen is not established and varies among practitioners.

Complications and Outcomes

Given that interventions are being performed in the venous system, significant bleeding is rare, especially given that recanalization is being performed in areas with very slow or no flow. Access site oozing is fairly common, especially given the intra and postprocedural anticoagulation necessary to keep the recanalized segments open. However, it can usually be controlled with manual compression. Patients may experience significant pain during and after the procedure in the stented and angioplastied regions. Stent migration is rare in experienced hands and may be reduced with appropriate attention to careful stent sizing. Patients should be cautioned that the procedure may not be technically successful, especially in long-standing occlusions, and that reintervention may be necessary given that between 15% and 40% of patients who undergo such procedures require a repeat procedure within 4 years.^{71,72}

Primary patency for stents deployed in iliofemoral segment postthrombotic veins is approximately 70% to 80%, and primary assisted and secondary patency are as high as 90% to 95%.⁷³⁻⁷⁶ Clinical outcomes are most improved for patients with more severe disease (C4–C6 in the CEAP classification), with greater than 50% resolution of venous dermatitis and ulcers after endovascular treatment.⁷⁷ A single-center study demonstrated an 80% complete or partial response to endovascular techniques (both deep and superficial) in patients with established PTS.⁷¹

However, it should be noted that robust, prospective, controlled studies are not available and that patients in the series were highly selected. The ongoing NIH-funded multicenter randomized controlled C-TRACT (Chronic Venous Thrombosis: Relief with Adjunctive Catheter-Directed Therapy) trial seeks to clarify these questions and definitively evaluate efficacy of endovascular stenting in iliofemoral occlusive disease compared with optimal medical therapy alone.⁷⁸

ACUTE PULMONARY EMBOLISM

EPIDEMIOLOGY AND CLASSIFICATION

Pulmonary embolism kills between 100,000 and 180,000 people in the United States per year, representing the third leading cause of cardiovascular mortality.⁷⁹⁻⁸¹ Although low-risk patients have a less than 1% mortality rate and are well treated with heparin alone, patients with massive or submassive PE have 20% to 50% and 2% to 3% mortality rates, respectively, despite full anticoagulation.⁸²⁻⁸⁴ The poorer outcomes of these higher risk subgroups led clinicians to consider escalating therapy with intravenous (IV) thrombolytics, catheter-based therapies, or surgical embolectomy.

Acute PE presentation is heterogeneous, ranging from asymptomatic to sudden death. Stratification into distinct risk categories is helpful when considering prognosis and therapeutic options. The American Heart Association (AHA) issued a guidance document in 2011 that defined the terms *massive*, *submassive*, and *low risk* signifying 30-day risk of death from PE.⁸³ A similar model was developed by the European Society of Cardiology (ESC) in 2014⁸⁵ and updated in 2019.⁸⁶ A massive PE (AHA) or a high-risk PE (ESC) is defined by sustained hypotension with systolic blood pressure less than 90 mm Hg or a decrease of more than 40 mm Hg for at least 15 minutes or one that requires pressor support.⁸³ Submassive (AHA) or intermediate-risk (ESC) PE is defined by the presence of right ventricular (RV) strain, dysfunction, or ischemia without hypotension. The ESC model requires intermediate-risk patients to have a simplified Pulmonary Embolism Severity Index (PESI) score of at least 1 (i.e., age older than 80 years, cancer, chronic respiratory disease or cardiac disease, heart rate > 11 beats/min, systolic blood pressure <100 mm Hg or oxygen saturation <90%) independent of RV strain. RV strain includes ventricular dysfunction diagnosed by CTA (RV/LV ratio >0.9) or by echocardiography. Evidence of RV injury is detected by increases in cardiac biomarkers (troponin and brain natriuretic peptide). The ESC model subdivides intermediate-risk patients into intermediate high risk, those with both RV dysfunction on imaging and RV injury with elevated biomarkers, and intermediate low risk, those with only one or neither finding. Finally, low-risk PE, defined by both AHA and ESC guidelines, does not meet criteria for submassive or intermediate-risk or massive or high-risk PE (i.e., no hypotension or heart strain).

All currently available risk stratification paradigms have important limitations. Although stratification proves to be a valuable aid in decision making, meticulous clinical

assessment should continue to drive treatment approaches. Future areas in prognostication include evaluation of additional hemodynamic variables (heart rate, oxygen saturation, respiratory rate, and so on), biomarker variables (e.g., lactate, arterial pH, glomerular filtration rate), and echocardiographic measurements (e.g., tricuspid annular plane systolic excursion, RV cardiac performance index, RV outflow track acceleration-deceleration times).⁸¹

TREATMENT ESCALATION FOR MASSIVE PULMONARY EMBOLISM

Given the high mortality rates for massive PE, most physicians and guidance documents agree that treatment escalation is prudent.^{2,83} The best treatment has not been established, however, because strong data are lacking. Systemic thrombolytics were associated with a lower composite endpoint of death and recurrent PE in a meta-analysis conducted in 2004.⁸⁷ However, they are also associated with a 20% major bleeding rate.⁸⁸ Surgical embolectomy is a viable option either as a rescue treatment for failed systemic thrombolysis or as a primary therapy for a patient in extremis.⁸⁹⁻⁹² Studies analyzing surgical embolectomy are nonrandomized and underpowered, making analysis of its benefit inconclusive; however, the ability to add extracorporeal membrane oxygenation in the operating room allows for advanced care of massive PE patients with the gravest prognosis.

Catheter-directed techniques offer several potential advantages. First, the morbidity and potential mortality associated with a sternotomy in hemodynamically unstable patients are avoided. Second, in patients with a high risk of bleeding from systemic lysis, flow can be restored with little or no thrombolytic agent. In a meta-analysis conducted by Kuo et al.,⁹³ catheter-directed massive PE treatment resulted in an 86% survival to discharge. It should be noted that the studies comprising this meta-analysis were most commonly retrospective without control arms and that publication bias could reduce reporting of patients with poor outcomes. The paucity of high-quality data can be explained by the baseline low incidence of high risk PE as well as a critically ill population that requires flexibility for multiple different treatment approaches. In this setting, nonrandomized prospective studies of current and newer devices are reasonable when assessing clinical effectiveness.

The endovascular strategy in the setting of massive PE is to restore flow through the pulmonary artery to improve left-sided filling pressures. Thus, mechanical clot maceration (Figure 26.8) and aspiration in combination with local delivery of a thrombolytic effectively reduce clot burden. Maceration can be accomplished by rotating a pigtail catheter within the thrombus or by using an automated mechanical device. Aspiration, originally performed through 7- to 10-Fr catheter, can now be performed through large-bore devices ranging from 12 to 24 Fr in size. Aspiration can also be performed in refractory cases after catheter-based thrombolysis. If the patient is a candidate, prolonged lytic infusion after these mechanical maneuvers can also reduce thrombus burden.

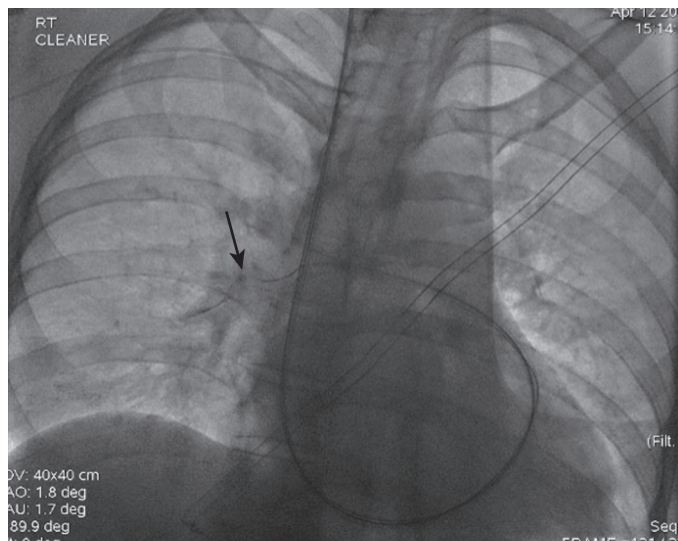


FIGURE 26.8 Mechanical clot maceration with a rotating thrombectomy device (arrow) in a patient with a massive pulmonary embolism.

TREATMENT ESCALATION FOR SUBMASSIVE PULMONARY EMBOLISM

The submassive group, representing up to 40% of acute PEs, is particularly challenging for clinicians because there are considerable differences of opinion regarding if, when, and how treatment escalation should occur. On the one hand, patients with submassive PEs are normotensive and therefore momentarily compensated. On the other, they have evidence of right heart strain, dysfunction, or ischemia, all of which are associated with higher mortality rates and clinical deterioration than low-risk PE.^{94,95} In essence, whether a patient will stabilize on heparin alone or will spiral toward progressive obstruction of the pulmonary arterial bed and exceed the threshold of RV tolerance is difficult to predict. Moreover, there is concern about the development of chronic dyspnea and exercise intolerance in patients with substantial residual clot burden who are treated with heparin alone.⁹⁶⁻⁹⁸ Although the prospective evaluation of long-term outcomes after pulmonary embolism (ELOPE) study demonstrated only 2% to 5% of hospitalized patients with incident PE develop chronic thromboembolic pulmonary hypertension, nearly 50% had reduced peak oxygen consumption on cardiopulmonary exercise testing; these patients also had reduced functional status and poorer quality of life.⁹⁹ Although concerning, it is unclear whether escalation of treatment prevents these changes. Compounding the complexity of escalating treatment in this subgroup is the fact that each strategy carries risk, invasiveness, inconvenience, and added costs. Society guideline documents do not give strong recommendations, reflecting the paucity of evidence to support one treatment over another.^{2,83}

The rapidly evolving landscape of treatment escalation for patients with acute PE has advanced the knowledge of submassive PE treatment; however, significant knowledge gaps remain. Surgical embolectomy has been explored; however, because of considerable morbidity, it is infrequently the first-line treatment.¹⁰⁰ The pulmonary embolism thrombolysis (PEITHO) trial studied IV thrombolysis in a

randomized fashion, demonstrating a net benefit in the primary combined endpoint of death and hemodynamic deterioration at 7 days in the group treated with IV thrombolytics plus anticoagulation compared with placebo plus anticoagulation, driven by increased hemodynamic deterioration in the placebo group.⁸⁴ However, this trial demonstrated a statistically significant increase in intracranial hemorrhage (2%) and major bleeding (11.5%) compared with the anticoagulation only group, (0.2% and 2.4%, respectively).⁸⁴ Catheter-based thrombolysis and thrombectomy devices have since garnered interest because of the limitations of anticoagulation and systemic thrombolysis.

Catheter-directed thrombolysis attempts to theoretically improve the safety profile of thrombolytic delivery by administering the agent directly into the thrombus, allowing for lower doses. The goal is to achieve similar or improved effectiveness compared with systemic thrombolysis while decreasing risk of major and intracranial bleeding. ULtrasound Accelerated Thrombolysis of PulMonArY Embolism (ULTIMA), the first randomized trial to study ultrasound-assisted catheter-directed thrombolysis (USAT) using the EKOS catheter (Boston Sci), demonstrated lower 24-hour RV/LV ratio and better 3-month RV function in the catheter-treated group than the heparin-only group, with no major or intracranial bleeding and 10% minor bleeding.¹⁰¹ Subsequently, the submassive and massive pulmonary embolism treatment with ultrasound accelerated thrombolysis therapy (SEATTLE II) trial evaluated the EKOS (EKOS Corp.) in a prospective single-arm study and found a statistically significant reduction of 25% in the RV/LV ratio 48 hours after initiation of USAT in the setting of massive and submassive PE with no intracranial or fatal bleeding.¹⁰² Optimum duration of acoustic pulse thrombolysis procedure in acute pulmonary embolism (OPTALYSE-PE) demonstrated comparable reduction in RV/LV ratio in patients among four different infusion protocols with the use of ultrasound-assisted CDT (EKOS, EKOS Corp.).¹⁰³ However, standard vs. ultrasound-assisted catheter thrombolysis for submassive pulmonary embolism (SUNSET-SPE), the first randomized controlled trial to compare USAT versus standard CDT, demonstrated similar reduction in pulmonary arterial thrombus scores with standard CDT and possibly a greater reduction of RV/LV ratio than USAT.¹⁰⁴ It is noted, however, criticisms of the study were the lack of standardization of dose regimens across the two groups and low power of the study.¹⁰⁵ The benefit of USAT over standard CDT remains unclear.

Alternatively, concerns of bleeding have led to development of catheter-based thrombectomy in attempts to offer mechanical relief of pulmonary outflow obstruction without the use of thrombolytics. The data for catheter-based thrombectomy are restricted to single-arm prospective studies focused on surrogate endpoints such as RV/LV ratio improvement. The FlowTrier pulmonary embolectomy clinical study (FLARE) study evaluated the safety and efficacy of the FlowTrier System (Inari Medical) involving 16- to 24-Fr aspiration catheters in patients with acute submassive PE and demonstrated a 0.39 reduction in RV/LV ratio 48 hours after the procedure.¹⁰⁶ Evaluating the safety and efficacy of the Indigo Aspiration System in acute

TABLE 26.4 Pulmonary Embolism Catheter-Directed Therapy: Comparative Studies

TRIAL	PATIENTS (N)	TREATMENT	COMPARATOR	FOLLOW-UP (DAYS)	INTERMEDIATE RISK PE, N (%)	HIGH RISK PE, N (%)	EFFICACY	SAFETY
PEITHO 2014 ⁸⁴	1006	Tenecteplase (30–50mg)	Heparin, LMWH, and fondaparinux	30	1005 (100)	0	Death at 7 d: • tPA, 2.6 • Placebo, 5.6	tPA: • ICH: 2% • Major bleed: 6.3%
ULTIMA 2013 ¹⁰¹	59	tPA-USAT (20 mg) (EKOS)	Heparin	90	59 (100)	0	RV/LV at 24 h: • tPA, –0.29 • Heparin, –0.03	tPA: one death, three minor bleeds
SEATTLE II 2015 ¹⁰²	150	tPA-USAT (24 mg) (EKOS)	Single arm	30	119 (79)	31 (21)	RV/LV at 48 h: –0.42	Major bleed: 10% Death: 2.7%
PERFECT 2015 ¹⁰⁸	101	tPA or urokinase, CDL (variable dosing mean, 28 mg of tPA)	Single arm	30	73 (72)	28 (28)	PASP: 51.17 mm Hg ± 14.06 mm Hg to 37.23 mm Hg ± 15.81 mm Hg	Major bleed: 0%
OPTALYSE 2018 ¹⁰³	101	tPA-USAT EKOS (8–24 mg)	Four tPA dose protocols	30	101 (100)	0	RV/LV: reduced in all arms	Major bleed: 4% Death at 30 d: 1% Death at 1 y: 2%
FLARE 2019 ¹⁰⁶	106	FlowTriever	Single arm	30	104 (100)	0	RV/LV at 48 h: –0.38	Major bleed: 1.0% Death: 1.0%
EXTRACT PE 2021 ¹⁰⁷	119	Indigo CAT 8	Single arm	30	119 (100)	0	RV/LV at 48 h: –0.43	Major bleed: 1.7% Death: 2.5%
SUNSET PE 2021 ¹⁰⁴	81	USAT	CDT	90	81 (100)	0	No significant difference in thrombus reduction RV/LV at 48 h: • USAT: –0.37 • CDT: –0.59	Major bleed: 4% USAT: 4% CDT: 0% Death: %0 both

CDL, catheter directed thrombolysis; CDT, catheter-directed thrombolysis; EXTRACT PE, Evaluating the safety and efficacy of the Indigo Aspiration System in acute pulmonary embolism; FLARE, FlowTriever pulmonary embolectomy clinical study; LMWH, low-molecular-weight heparin; OPTALYSE, Optimum duration of acoustic pulse thrombolysis procedure in acute pulmonary embolism; PASP, pulmonary artery systolic pressure; PE, pulmonary embolism; PEITHO, pulmonary embolism thrombolysis; RV/LV, right ventricular-to-left ventricular size ratio; SEATTLE, submassive and massive pulmonary embolism treatment with ultrasound accelerated thrombolysis therapy; SUNSET PE, standard vs. ultrasound-assisted catheter thrombolysis for submassive pulmonary embolism; tPA, tissue plasminogen activator; ULTIMA, ULTrasound Accelerated Thrombolysis of PulMonArY Embolism; USAT, ultrasound-assisted catheter-directed thrombolysis.

pulmonary embolism (EXTRACT-PE) trial examined the safety and efficacy of the Indigo CAT 8-Fr aspiration thrombectomy system (Penumbra,) and similarly demonstrated an RV/LV ratio reduction of 0.43.¹⁰⁷ Despite similarities in design and collection of data from these two independent studies, questions regarding the long-term clinical impact and benefit remain. A summary of these trials can be seen in Table 26.4.

The ideal candidate for catheter-directed PE lysis or thrombectomy has central thrombus through which an infusion catheter or aspiration catheter can be placed (Figure 26.9). If the clot is too peripheral such that the catheter cannot be embedded within the thrombus, alternative strategies should be considered. Procedurally, venous access can be from the common femoral vein or internal jugular vein. Pulmonary arterial pressure measurements should be performed to establish a baseline and to determine the injection rate for angiography. Angiography can be performed from the main pulmonary artery or the right and left main branches; the latter allows for better delineation of the clot burden and location. Many elect to forego formal pulmonary angiography, given the high quality of CTA at depicting amount and location of PA thrombus. A wire is then guided through the clot, over which a multi-sidehole infusion catheter is advanced into the thrombus. Similarly, a large-bore aspiration catheter can be advanced over a guidewire to the margin of the

clot. For thrombolysis, a bolus of thrombolytic can be given, after which an infusion is begun. If bilateral emboli are present, a second infusion catheter can be placed on the contralateral side. For catheter thrombectomy, continuous or intermittent aspiration can be applied while maneuvering the catheter until on-table hemodynamic endpoints are achieved. Regardless of treatment method, IV heparin should be continued; although some argue that subtherapeutic doses should be used to reduce the risk of bleeding, others maintain that preventing mortality from submassive PE requires therapeutic anticoagulation.

To date, no trials have been carried out that have sufficient power to assess potential benefits in short-term mortality rates or hemodynamic decompensation when comparing CDT with systemic thrombolysis. Because of this difficulty, the majority of catheter-based therapy trials and studies have focused on surrogate markers such as RV/LV ratio to assess outcomes. This marker has been shown in observational studies to indicate a significantly elevated 30-day mortality rate when RV/LV is greater than 0.9.¹⁰⁹ A frequent criticism, however, is whether reduction in the ratio is an appropriate metric for mortality rate or for positive outcomes after intervention. Future studies involving clinical outcomes of functional status, exercise tolerance, and subjective quality of life metrics are needed to assess the long-term benefits of catheter-based therapies.

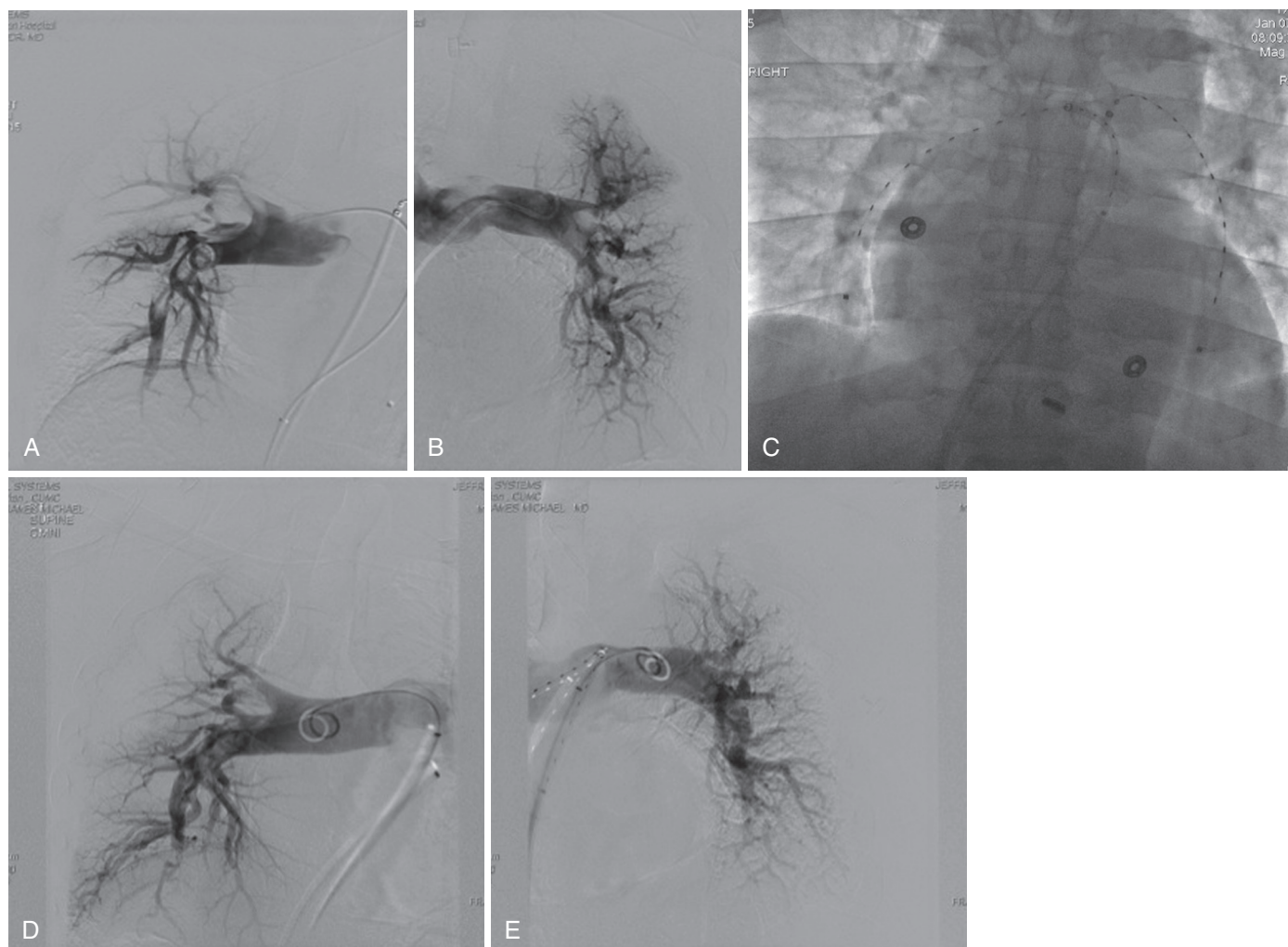


FIGURE 26.9 Right (A) and left (B) pulmonary angiograms demonstrating thrombus in the right upper and lower lobe branches and left lingular and lower lobe branches. C, Placement of bilateral ultrasound-assisted infusion catheters into lower lobe thrombi. Infusion occurred over 20 hours. Right (D) and left (E) pulmonary angiograms after lytic infusion demonstrating markedly improved perfusion. The pulmonary systolic pressure was reduced from 56 to 36 mm Hg.

PATIENT FOLLOW-UP

Patients with massive and submassive PE should continue to be followed as outpatients after discharge from their acute event. Repeat echocardiography can document persistent RV dysfunction or the development of pulmonary hypertension.

Cardiopulmonary rehabilitation and appropriate pulmonary hypertension treatment can be initiated as necessary. A multidisciplinary team including hematologists, cardiologists, interventionalists, and pulmonologists ensures optimal care for these patients. The duration and type of anticoagulation can be monitored, and if an IVC filter was placed during the hospitalization, it can be removed if appropriate and feasible.

Visit Elsevier eBooks+ to access the complete list of references.

SELECTED REFERENCES

- Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl):e419S-e496S.
- Kaufman JA, Barnes GD, Chaer RA, et al. Society of Interventional Radiology Clinical Practice Guideline for Inferior Vena Cava Filters in the Treatment of Patients with Venous Thromboembolic Disease: developed in collaboration with the American College of Cardiology, American College of Chest Physicians, American College of Surgeons Committee on Trauma, American Heart Association, Society for Vascular Surgery, and Society for Vascular Medicine. *J Vasc Interv Radiol*. 2020;31(10):1529-1544.
- Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. *N Engl J Med*. 1998;338(7):409-415.
- Mismetti P, Laporte S, Pellerin O, et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. *JAMA*. 2015;313(16):1627-1635.
- Kelkar AH, Rajasekhar A. Inferior vena cava filters: a framework for evidence-based use. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):619-628.
- Kahn SR, Shbaklo H, Lamping DL, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. *J Thromb Haemost*. 2008;6(7):1105-1112.
- Roumen-Klappe EM, Janssen MC, Van Rossum J, et al. Inflammation in deep vein thrombosis and the development of post-thrombotic syndrome: a prospective study. *J Thromb Haemost*. 2009;7(4):582-587.
- Brandjes DP, Büller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet*. 1997;349(9054):759-762.
- Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med*. 2004;141(4):249-256.



32. Kahn SR, Shbaklo H, Shapiro S, et al. Effectiveness of compression stockings to prevent the post-thrombotic syndrome (the SOX Trial and Bio-SOX biomarker substudy): a randomized controlled trial. *BMC Cardiovasc Disord.* 2007;7:21.
36. Goldhaber SZ, Meyerovitz MF, Green D, et al. Randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis. *Am J Med.* 1990;88(3):235-240.
41. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv.* 2020;4(19):4693-4738.
46. Baker R, Samuels S, Benenati JF, et al. Ultrasound-accelerated vs standard catheter-directed thrombolysis—a comparative study in patients with iliofemoral deep vein thrombosis. *J Vasc Interv Radiol.* 2012;23(11):1460-1466.
48. Kim HS, Patra A, Paxton BE, et al. Adjunctive percutaneous mechanical thrombectomy for lower-extremity deep vein thrombosis: clinical and economic outcomes. *J Vasc Interv Radiol.* 2006;17(7):1099-1104.
49. Comerota AJ, Kearon C, Julian JA, et al. Endovascular thrombus removal for acute iliofemoral deep vein thrombosis: analysis from a stratified multicenter randomized trial. *Circulation.* 2019;139(9):1162-1173.
50. Kearon C, Gu C-S, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis in acute femoral-popliteal deep vein thrombosis: analysis from a stratified randomized trial. *Thromb Haemost.* 2019;119(4):633-644.
51. Comerota AJ, Throm RC, Mathias SD, et al. Catheter-directed thrombolysis for iliofemoral deep venous thrombosis improves health-related quality of life. *J Vasc Surg.* 2000;32(1):130-137.
53. Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. *Eur J Vasc Endovasc Surg.* 2002;24(3):209-214.
54. Enden T, Haig Y, Klöw N-E, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet.* 2012;379(9810):31-38.
55. Vedantham S, Goldhaber SZ, Kahn SR, et al. Rationale and design of the ATTRACT Study: a multicenter randomized trial to evaluate pharmacomechanical catheter-directed thrombolysis for the prevention of postthrombotic syndrome in patients with proximal deep vein thrombosis. *Am Heart J.* 2013;165(4):523-530.e3.
56. Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. *N Engl J Med.* 2017;377(23):2240-2252.
57. Magnuson EA, Chinnakondepalli K, Vilain K, et al. Cost-effectiveness of pharmacomechanical catheter-directed thrombolysis vs. standard anticoagulation in patients with proximal deep-vein thrombosis: results from the ATTRACT Trial. *Circ Cardiovasc Qual Outcomes.* 2019;12(10):e005659.
58. Kahn SR, Julian JA, Kearon C, et al. Quality of life after pharmacomechanical catheter-directed thrombolysis for proximal deep venous thrombosis. *J Vasc Surg Venous Lymphat Disord.* 2020;8(1):8-23.e18.
59. Weinberg I, Vedantham S, Salter A, et al. Relationships between the use of pharmacomechanical catheter-directed thrombolysis, sonographic findings, and clinical outcomes in patients with acute proximal DVT: results from the ATTRACT multicenter randomized trial. *Vasc Med.* 2019;24(5):442-451.
60. Raffetto JD. Inflammation in chronic venous ulcers. *Phlebology.* 2013;28(suppl 1):61-67.
64. Kahn SR, Shrier I, Shapiro S, et al. Six-month exercise training program to treat post-thrombotic syndrome: a randomized controlled two-centre trial. *CMAJ.* 2011;183(1):37-44.
67. Kuo WT, Odegaard JI, Rosenberg JK, et al. Excimer laser-assisted removal of embedded inferior vena cava filters: a single-center prospective study. *Circ Cardiovasc Interv.* 2013;6(5):560-566.
69. Kibbe MR, Ujiki M, Goodwin AL, et al. Iliac vein compression in an asymptomatic patient population. *J Vasc Surg.* 2004;39(5):937-943.
71. Nayak L, Hildebolt CF, Vedantham S. Postthrombotic syndrome: feasibility of a strategy of imaging-guided endovascular intervention. *J Vasc Interv Radiol.* 2012;23(9):1165-1173.
72. Raju S, Neglén P. Percutaneous recanalization of total occlusions of the iliac vein. *J Vasc Surg.* 2009;50(2):360-368.
73. Neglén P, Hollis KC, Olivier J, et al. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. *J Vasc Surg.* 2007;46(5):979-990.
74. Dake MD, O'Sullivan G, Shammass NW, et al. Three-year results from the venovo venous stent study for the treatment of iliac and femoral vein obstruction. *Cardiovasc Intervent Radiol.* 2021;44(12):1918-1929. Erratum in: *Cardiovasc Intervent Radiol.* 2021 Oct 19.
75. Razavi MK, Black S, Gagne P, et al. Pivotal study of endovenous stent placement for symptomatic iliofemoral venous obstruction. *Circ Cardiovasc Interv.* 2019;12(12):e008268.
76. Murphy E, Sapoval M, Dexter DJ, et al. Pivotal study evaluating the safety and effectiveness of the Abre venous self-expanding stent system in patients with symptomatic iliofemoral venous outflow obstruction. *Circ Cardiovasc Interv.* 2022;15(2):e010960.
78. Thukral S, Vedantham S. Catheter-based therapies and other management strategies for deep vein thrombosis and post-thrombotic syndrome. *J Clin Med.* 2020;9(5):1439.
81. Giri J, Sista AK, Weinberg I, et al. Interventional therapies for acute pulmonary embolism: current status and principles for the development of novel evidence: a scientific statement from the American Heart Association. *Circulation.* 2019;140(20):e774-e801.
82. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet.* 1999;353(9162):1386-1389.
83. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation.* 2011;123(16):1788-1830.
84. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med.* 2014;370(15):1402-1411.
86. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J.* 2019;54(3):1901647.
97. Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). *Am J Cardiol.* 2013;111(2):273-277.
99. Kahn SR, Hirsch AM, Akaberi A, et al. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE prospective cohort study. *Chest.* 2017;151(5):1058-1068.
102. Piazza G, Hohlfelder B, Jaff MR, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. *JACC Cardiovasc Interv.* 2015;8(10):1382-1392.
103. Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE trial. *JACC Cardiovasc Interv.* 2018;11(14):1401-1410.
104. Avgerinos ED, Jaber W, Lacomis J, et al. Randomized trial comparing standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism: the SUNSET sPE trial. *JACC Cardiovasc Interv.* 2021;14(12):1364-1373. Erratum in: *JACC Cardiovasc Interv.* 2021;14(19):2194.
105. Sista AK. Is it time to sunset ultrasound-assisted catheter-directed thrombolysis for submassive PE? *JACC Cardiovasc Interv.* 2021;14(12):1374-1375.
106. Tu T, Toma C, Tapson VF, et al. A prospective, single-arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism: the FLARE study. *JACC Cardiovasc Interv.* 2019;12(9):859-869.
107. Sista AK, Horowitz JM, Tapson VF, et al. Indigo aspiration system for treatment of pulmonary embolism: results of the EXTRACT-PE trial. *JACC Cardiovasc Interv.* 2021;14(3):319-329.
108. Kuo WT, Banerjee A, Kim PS, et al. Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis (PERFECT): initial results from a prospective multicenter registry. *Chest.* 2015;148(3):667-673.

REFERENCES

- Meissner MH. Indications for platelet aggregation inhibitors after venous stents. *Phlebology*. 2013;28(suppl 1):91-98.
- Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl):e419S-e496S.
- EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510.
- Kaufman JA, Barnes GD, Chaer RA, et al. Society of Interventional Radiology Clinical Practice Guideline for Inferior Vena Cava Filters in the Treatment of Patients with Venous Thromboembolic Disease: developed in collaboration with the American College of Cardiology, American College of Chest Physicians, American College of Surgeons Committee on Trauma, American Heart Association, Society for Vascular Surgery, and Society for Vascular Medicine. *J Vasc Interv Radiol*. 2020;31(10):1529-1544.
- Desai KR, Pandhi MB, Seedial SM, et al. Retrievable IVC filters: comprehensive review of device-related complications and advanced retrieval techniques. *Radiographics*. 2017;37(4):1236-1245.
- Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. *N Engl J Med*. 1998;338(7):409-415.
- Mismetti P, Laporte S, Pellerin O, et al. PREPIC2 Study Group. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. *JAMA*. 2015;313(16):1627-1635.
- Kelkar AH, Rajasekhar A. Inferior vena cava filters: a framework for evidence-based use. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):619-628.
- Winokur RS, Bassik N, Madoff DC, Trost D. Radiologists' field guide to retrievable and convertible inferior vena cava filters. *AJR Am J Roentgenol*. 2019;213(4):768-777. Erratum in: *AJR Am J Roentgenol*. 2019;213(5):1174.
- Dake MD, Murphy TP, Krämer AH, et al. Final two-year outcomes for the Sentry Bioconvertible inferior vena cava filter in patients requiring temporary protection from pulmonary embolism. *J Vasc Interv Radiol*. 2020;31(2):221-230.e3.
- Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the post-thrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med*. 2008;149(10):698-707.
- Kahn SR, Shbaklo H, Lamping DL, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. *J Thromb Haemost*. 2008;6(7):1105-1112.
- Caprini JA, Botteman MF, Stephens JM, et al. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. *Value Health*. 2003;6(1):59-74.
- Olin JW, Beusterien KM, Childs MB, et al. Medical costs of treating venous stasis ulcers: evidence from a retrospective cohort study. *Vasc Med*. 1999;4(1):1-7.
- Roumen-Klappe EM, Janssen MC, Van Rossum J, et al. Inflammation in deep vein thrombosis and the development of post-thrombotic syndrome: a prospective study. *J Thromb Haemost*. 2009;7(4):582-587.
- Shbaklo H, Holcroft CA, Kahn SR. Levels of inflammatory markers and the development of the post-thrombotic syndrome. *Thromb Haemost*. 2009;101(3):505-512.
- Wakefield TW, Myers DD, Henke PK. Role of selectins and fibrinolysis in VTE. *Thromb Res*. 2009;123(suppl 4):S35-S40.
- Deroo S, Deatrack KB, Henke PK. The vessel wall: a forgotten player in post thrombotic syndrome. *Thromb Haemost*. 2010;104(4):681-692.
- Caps MT, Manzo RA, Bergelin RO, et al. Venous valvular reflux in veins not involved at the time of acute deep vein thrombosis. *J Vasc Surg*. 1995;22(5):524-531.
- Markel A, Manzo RA, Bergelin RO, et al. Valvular reflux after deep vein thrombosis: incidence and time of occurrence. *J Vasc Surg*. 1992;15(2):377-384; discussion 383-384.
- Shull KC, Nicolaides AN, Fernandes é Fernandes J, et al. Significance of popliteal reflux in relation to ambulatory venous pressure and ulceration. *Arch Surg*. 1979;114(11):1304-1306.
- Prandoni P, Frulla M, Sartor D, et al. Vein abnormalities and the post-thrombotic syndrome. *J Thromb Haemost*. 2005;3(2):401-402.
- Meissner MH, Manzo RA, Bergelin RO, et al. Deep venous insufficiency: the relationship between lysis and subsequent reflux. *J Vasc Surg*. 1993;18(4):596-605; discussion 606-608.
- Nicolaides AN, Hussein MK, Szendro G, et al. The relation of venous ulceration with ambulatory venous pressure measurements. *J Vasc Surg*. 1993;17(2):414-419.
- Welkie JF, Comerota AJ, Katz ML, et al. Hemodynamic deterioration in chronic venous disease. *J Vasc Surg*. 1992;16(5):733-740.
- Araki CT, Back TL, Padberg FT, et al. The significance of calf muscle pump function in venous ulceration. *J Vasc Surg*. 1994;20(6):872-877; discussion 878-879.
- Johnson BF, Manzo RA, Bergelin RO, Strandness DE Jr. Relationship between changes in the deep venous system and the development of the postthrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one- to six-year follow-up. *J Vasc Surg*. 1995;21(2):307-312; discussion 313.
- van Dongen CJ, Prandoni P, Frulla M, et al. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. *J Thromb Haemost*. 2005;3(5):939-942.
- Douketis JD, Crowther MA, Foster GA, et al. Does the location of thrombosis determine the risk of disease recurrence in patients with proximal deep vein thrombosis? *Am J Med*. 2001;110(7):515-519.
- Brandjes DP, Büller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet*. 1997;349(9054):759-762.
- Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med*. 2004;141(4):249-256.
- Kahn SR, Shbaklo H, Shapiro S, et al. Effectiveness of compression stockings to prevent the post-thrombotic syndrome (the SOX Trial and Bio-SOX biomarker substudy): a randomized controlled trial. *BMC Cardiovasc Disord*. 2007;7:21.
- Hull RD, Marder VJ, Mah AF, et al. Quantitative assessment of thrombus burden predicts the outcome of treatment for venous thrombosis: a systematic review. *Am J Med*. 2005;118(5):456-464.
- Plate G, Akesson H, Einarsson E, et al. Long-term results of venous thrombectomy combined with a temporary arterio-venous fistula. *Eur J Vasc Surg*. 1990;4(5):483-489.
- Goldhaber SZ, Buring JE, Lipnick RJ, Hennekens CH. Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented acute deep venous thrombosis. *Am J Med*. 1984;76(3):393-397.
- Goldhaber SZ, Meyerovitz MF, Green D, et al. Randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis. *Am J Med*. 1990;88(3):235-240.
- Meyerovitz MF, Polak JF, Goldhaber SZ. Short-term response to thrombolytic therapy in deep venous thrombosis: predictive value of venographic appearance. *Radiology*. 1992;184(2):345-348.
- Schwieder G, Grimm W, Siemens HJ, et al. Intermittent regional therapy with rt-PA is not superior to systemic thrombolysis in deep vein thrombosis (DVT)—a German multicenter trial. *Thromb Haemost*. 1995;74(5):1240-1243.
- Mewissen MW, Seabrook GR, Meissner MH, et al. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. *Radiology*. 1999;211(1):39-49.
- Semba CP, Dake MD. Iliofemoral deep venous thrombosis: aggressive therapy with catheter-directed thrombolysis. *Radiology*. 1994;191(2):487-494.
- Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693-4738.
- Vedantham S, Thorpe PE, Cardella JF, et al. Quality improvement guidelines for the treatment of lower extremity deep vein thrombosis with use of endovascular thrombus removal. *J Vasc Interv Radiol*. 2006;17(3):435-447; quiz 448.
- Grunwald MR, Hofmann LV. Comparison of urokinase, alteplase, and reteplase for catheter-directed thrombolysis of deep venous thrombosis. *J Vasc Interv Radiol*. 2004;15(4):347-352.
- Shortell CK, Queiroz R, Johansson M, et al. Safety and efficacy of limited-dose tissue plasminogen activator in acute vascular occlusion. *J Vasc Surg*. 2001;34(5):854-859.
- Sugimoto K, Hofmann LV, Razavi MK, et al. The safety, efficacy, and pharmacoeconomics of low-dose alteplase compared with urokinase for catheter-directed thrombolysis of arterial and venous occlusions. *J Vasc Surg*. 2003;37(3):512-517.
- Baker R, Samuels S, Benenati JF, et al. Ultrasound-accelerated vs standard catheter-directed thrombolysis—a comparative study in patients with iliofemoral deep vein thrombosis. *J Vasc Interv Radiol*. 2012;23(11):1460-1466.
- Parikh S, Motarjeme A, McNamara T, et al. Ultrasound-accelerated thrombolysis for the treatment of deep vein thrombosis: initial clinical experience. *J Vasc Interv Radiol*. 2008;19(4):521-528.
- Kim HS, Patra A, Paxton BE, et al. Adjunctive percutaneous mechanical thrombectomy for lower-extremity deep vein thrombosis: clinical and economic outcomes. *J Vasc Interv Radiol*. 2006;17(7):1099-1104.
- Comerota AJ, Kearon C, Gu C-S, et al. Endovascular thrombus removal for acute iliofemoral deep vein thrombosis: analysis from a stratified multicenter randomized trial. *Circulation*. 2019;139(9):1162-1173.
- Kearon, Clive, Gu C-S, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis in acute femoral-popliteal deep vein thrombosis: analysis from a stratified randomized trial. *Thromb Haemost*. 2019;119(4):633-644.
- Comerota AJ, Thom RC, Mathias SD, et al. Catheter-directed thrombolysis for iliofemoral deep venous thrombosis improves health-related quality of life. *J Vasc Surg*. 2000;32(1):130-137.
- AbuRahma AF, Perkins SE, Wulu JT, Ng HK. Iliofemoral deep vein thrombosis: conventional therapy versus lysis and percutaneous transluminal angioplasty and stenting. *Ann Surg*. 2001;233(6):752-760.
- Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. *Eur J Vasc Endovasc Surg*. 2002;24(3):209-214.
- Enden T, Haig Y, Kløw N-E, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet*. 2012;379(9810):31-38.
- Vedantham S, Goldhaber SZ, Kahn SR, et al. Rationale and design of the ATTRACT Study: a multicenter randomized trial to evaluate pharmacomechanical catheter-directed thrombolysis for the prevention of postthrombotic syndrome in patients with proximal deep vein thrombosis. *Am Heart J*. 2013;165(4):523-530.e3.



56. Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. *N Engl J Med*. 2017;377(23):2240-2252.
57. Magnuson EA, Vilain K, Kearon C, et al. Cost-effectiveness of pharmacomechanical catheter-directed thrombolysis vs. standard anticoagulation in patients with proximal deep-vein thrombosis: results from the ATTRACT Trial. *Circ Cardiovasc Qual Outcomes*. 2019;12(10):e005659.
58. Kahn SR, Julian JA, Kearon C, et al. Quality of life after pharmacomechanical catheter-directed thrombolysis for proximal deep venous thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2020;8(1):8-23.e18.
59. Weinberg I, Vedantham S, Salter A, et al. Relationships between the use of pharmacomechanical catheter-directed thrombolysis, sonographic findings, and clinical outcomes in patients with acute proximal DVT: results from the ATTRACT multicenter randomized trial. *Vasc Med*. 2019;24(5):442-451.
60. Raffetto JD. Inflammation in chronic venous ulcers. *Phlebology*. 2013;28(suppl 1):61-67.
61. Heit JA, Rooke TW, Silverstein MD, et al. Trends in the incidence of venous stasis syndrome and venous ulcer: a 25-year population-based study. *J Vasc Surg*. 2001;33(5):1022-1027.
62. Ginsberg JS, Magier D, Mackinnon B, et al. Intermittent compression units for severe post-phlebotic syndrome: a randomized crossover study. *CMAJ*. 1999;160(9):1303-1306.
63. O'Donnell MJ, McRae S, Kahn SR, et al. Evaluation of a venous-return assist device to treat severe postthrombotic syndrome (VENOPTS). A randomized controlled trial. *Thromb Haemost*. 2008;99(3):623-629.
64. Kahn SR, Shrier I, Shapiro S, et al. Six-month exercise training program to treat post-thrombotic syndrome: a randomized controlled two-centre trial. *CMAJ*. 2011;183(1):37-44.
65. Jost CJ, Gloviczki P, Cherry KJ Jr, et al. Surgical reconstruction of iliofemoral veins and the inferior vena cava for nonmalignant occlusive disease. *J Vasc Surg*. 2001;33(2):320-327; discussion 327-328.
66. Rimón U, Bensaid P, Golan G, et al. OptEase vena cava filter optimal indwelling time and retrievability. *Cardiovasc Intervent Radiol*. 2011;34(3):532-535.
67. Kuo WT, Odegaard JI, Rosenberg JK, et al. Excimer laser-assisted removal of embedded inferior vena cava filters: a single-center prospective study. *Circ Cardiovasc Interv*. 2013;6(5):560-566.
68. Hill DA, Goldstein N, Kuo EY. Vena cava filter fracture with migration to the pulmonary artery. *Ann Thorac Surg*. 2013;95(1):342-345.
69. Kibbe MR, Ujiki M, Goodwin AL, et al. Iliac vein compression in an asymptomatic patient population. *J Vasc Surg*. 2004;39(5):937-943.
70. Razavi MK, Hansch EC, Kee ST, et al. Chronically occluded inferior vena cavae: endovascular treatment. *Radiology*. 2000;214(1):133-138.
71. Nayak L, Hildebolt CF, Vedantham S. Postthrombotic syndrome: feasibility of a strategy of imaging-guided endovascular intervention. *J Vasc Interv Radiol*. 2012;23(9):1165-1173.
72. Raju S, Neglén P. Percutaneous recanalization of total occlusions of the iliac vein. *J Vasc Surg*. 2009;50(2):360-368.
73. Neglén P, Hollis KC, Olivier J, et al. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. *J Vasc Surg*. 2007;46(5):979-990.
74. Dake MD, O'Sullivan G, Shammass NW, et al. Three-year results from the venovo venous stent study for the treatment of iliac and femoral vein obstruction. *Cardiovasc Intervent Radiol*. 2021;44(12):1918-1929. Erratum in: *Cardiovasc Intervent Radiol*. 2021 Oct 19.
75. Razavi MK, Black S, Gagne P, Chiacchierini R, Nicolini P, Marston W, VIRTUS Investigators. Pivotal study of endovenous stent placement for symptomatic iliofemoral venous obstruction. *Circ Cardiovasc Interv*. 2019;12(12):e008268.
76. Murphy E, Gibson K, Sapoval M, et al. Pivotal study evaluating the safety and effectiveness of the Abre venous self-expanding stent system in patients with symptomatic iliofemoral venous outflow obstruction. *Circ Cardiovasc Interv*. 2022;15(2):e010960.
77. Raju S, Darcey R, Neglén P. Unexpected major role for venous stenting in deep reflux disease. *J Vasc Surg*. 2010;51(2):401-408; discussion 408.
78. Thukral S, Vedantham S. Catheter-based therapies and other management strategies for deep vein thrombosis and post-thrombotic syndrome. *J Clin Med*. 2020;9(5):1439.
79. Beckman MG, Hooper WC, Critchley SE, et al. Venous thromboembolism: a public health concern. *Am J Prev Med*. 2010;38(4 suppl):S495-S501.
80. White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(23 suppl 1):14-18.
81. Giri J, Sista AK, Weinberg I, et al. Interventional therapies for acute pulmonary embolism: current status and principles for the development of novel evidence: a scientific statement from the American Heart Association. *Circulation*. 2019;140(20):e774-e801.
82. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*. 1999;353(9162):1386-1389.
83. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation*. 2011;123(16):1788-1830.
84. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370(15):1402-1411.
85. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35(43):3033-3069. Erratum in: *Eur Heart J*. 2015;36(39):2666. Erratum in: *Eur Heart J*. 2015;36(39):2642.
86. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J*. 2019;54(3):1901647.
87. Wan S, Quinlan DJ, Agnelli G, et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation*. 2004;110(6):744-749.
88. Fiumara K, Kucher N, Fanikos J, et al. Predictors of major hemorrhage following fibrinolysis for acute pulmonary embolism. *Am J Cardiol*. 2006;97(1):127-129.
89. Ahmed P, Khan AA, Smith A, et al. Expedient pulmonary embolectomy for acute pulmonary embolism: improved outcomes. *Interact Cardiovasc Thorac Surg*. 2008;7(4):591-594.
90. Aymard T, Kadner A, Widmer A, et al. Massive pulmonary embolism: surgical embolectomy versus thrombolytic therapy—should surgical indications be revisited? *Eur J Cardiothorac Surg*. 2013;43(1):90-94; discussion 94.
91. Kadner A, Schmidli J, Schönhof F, et al. Excellent outcome after surgical treatment of massive pulmonary embolism in critically ill patients. *J Thorac Cardiovasc Surg*. 2008;136(2):448-451.
92. Zarrabi K, Zolghadrasli A, Ostovan MA, Azimifar A. Short-term results of retrograde pulmonary embolectomy in massive and submassive pulmonary embolism: a single-center study of 30 patients. *Eur J Cardiothorac Surg*. 2011;40(4):890-893.
93. Kuo WT, Gould MK, Louie JD, et al. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. *J Vasc Interv Radiol*. 2009;20(11):1431-1440.
94. Sanchez O, Trinquart L, Colombet I, et al. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. *Eur Heart J*. 2008;29(12):1569-1577.
95. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation*. 2007;116(4):427-433.
96. Kline JA, Steuerwald MT, Marchick MR, et al. Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure. *Chest*. 2009;136(5):1202-1210.
97. Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPE" Trial). *Am J Cardiol*. 2013;111(2):273-277.
98. Stevinson BG, Hernandez-Nino J, Rose G, et al. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. *Eur Heart J*. 2007;28(20):2517-2524.
99. Kahn SR, Hirsch AM, Akaberi A, et al. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE prospective cohort study. *Chest*. 2017;151(5):1058-1068.
100. Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. *J Thorac Cardiovasc Surg*. 2005;129(5):1018-1023.
101. Kucher N, Boekstegers P, Müller OJ, et al. Randomized controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation*. 2014;129(4):479-486.
102. Piazza G, Hohlfelder B, Jaff MR, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. *JACC Cardiovasc Interv*. 2015;8(10):1382-1392.
103. Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE trial. *JACC Cardiovasc Interv*. 2018;11(14):1401-1410.
104. Avgerinos ED, Jaber W, Lacomis J, et al. Randomized trial comparing standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism: the SUNSET sPE trial. *JACC Cardiovasc Interv*. 2021;14(12):1364-1373. Erratum in: *JACC Cardiovasc Interv*. 2021;14(19):2194.
105. Sista AK. Is it time to sunset ultrasound-assisted catheter-directed thrombolysis for submassive PE? *JACC Cardiovasc Interv*. 2021;14(12):1374-1375.
106. Tu T, Toma C, Tapson VF, et al. A prospective, single-arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism: the FLARE study. *JACC Cardiovasc Interv*. 2019;12(9):859-869.
107. Sista AK, Horowitz JM, Tapson VF, et al. Indigo aspiration system for treatment of pulmonary embolism: results of the EXTRACT-PE trial. *JACC Cardiovasc Interv*. 2021;14(3):319-329.
108. Kuo WT, Banerjee A, Kim PS, et al. Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis (PERFECT): initial results from a prospective multicenter registry. *Chest*. 2015;148(3):667-673.
109. Schoepf UJ, Kucher N, Kipfmüller F, Quiroz R, Costello P, Goldhaber SZ. Right ventricular enlargement on chest computed tomography: a predictor of early death in acute pulmonary embolism. *Circulation*. 2004;110(20):3276-3280.



EPIDEMIOLOGY AND RISK FACTORS OF CHRONIC VENOUS DISEASE, 493

VENOUS ANATOMY AND PHYSIOLOGY, 494

Superficial Veins of the Lower Limb, 494

Perforators of the Lower Limb, 497

Deep Venous System, 498

Physiology of the Venous System, 498

ETIOLOGY AND PATHOPHYSIOLOGY OF CHRONIC VENOUS INSUFFICIENCY, 498

EVALUATION AND CLASSIFICATION OF PATIENTS WITH CHRONIC VENOUS INSUFFICIENCY, 499

ANATOMIC AND PHYSIOLOGIC TESTING OF CHRONIC VENOUS INSUFFICIENCY, 501

Duplex Venous Ultrasonography of the

Lower Limb, 501

Plethysmography, 502

TREATMENT OF SUPERFICIAL CHRONIC VENOUS INSUFFICIENCY, 502

Compression Therapy, 504

Endovascular Heat Ablative Therapies, 504

Nonthermal Ablative Therapies, 506

Phlebectomy, 508

Surgical Vein Stripping, 508

Pharmacologic Management of Chronic Venous Insufficiency, 508

ENDOVASCULAR MANAGEMENT OF VENOUS ULCERATIONS, 509

DEEP VENOUS VALVES, 510

CONCLUSIONS, 511

EPIDEMIOLOGY AND RISK FACTORS OF CHRONIC VENOUS DISEASE

Chronic venous disease (CVD) is a condition that affects the superficial and deep venous systems, resulting in venous hypertension and a cascade of biochemical and vessel wall changes that lead to a spectrum of pathologies ranging from telangiectasias to venous stasis ulcerations. Chronic venous insufficiency (CVI) is an advanced form of CVD, generally presenting with lower extremity edema, trophic skin changes, and venous ulcerations. This chronic condition has often been neglected by providers because of its chronic and subtle progression and the lack of emphasis on its clinical presentation and pathophysiology within the general medical education curriculum. Unfortunately, CVI has a major impact on society, negatively affecting the quality of life of patients and consuming large health care dollars and resources.

Chronic venous disease is highly prevalent in the United States and western Europe, but its true prevalence is unknown because of variability in the definition of the disease and methodology of evaluation. An estimated 25 million people in the United States have CVD, with 2 million to 6 million having CVI, and nearly 500,000 have venous stasis ulceration.¹ In the Edinburgh Vein Study, a cross-sectional study of a random sample of 1566 participants, the prevalences of telangiectasias and reticular veins were approximately 80% and 85%, of varicose veins were 40% and 16%, and of ankle edema were 7% and 16% in men and women, respectively.² Various studies have shown that the prevalence of varicose veins ranged from 2% to 56% in men and 1% to 60% in women.³ This prevalence increases with age. In the Edinburgh study, the overall prevalence of venous reflux by duplex ultrasonography (DU) was 9.4% of men and 6.6% of women but rose to 21.2% in men and

12.0% in women older than the age of 50 years.⁴ Similarly, trophic skin changes seem to increase with age with a prevalence of 1.8% in young women 30 to 39 years of age and 20.7% in women older than the age of 70 years.⁵ Finally, venous ulcers occur in approximately 1% of the general population and also increase with age.^{2,6,7}

The incidence of CVD or its occurrence within a defined period of time has been evaluated in the Framingham Study.⁸ Every second year and over a period of 16 years, participants were examined for the appearance of varicose veins. The 1-year incidence rates of varicose veins were found to be 1.97% for men and 2.6% for women. In the Edinburgh Vein Study,⁹ the annual incidence rate in developing varicose veins was 1.4%, with incidence rates similar in men and women.

Several studies have suggested that women have a higher incidence of CVD, but this has not been shown in more recent studies.^{9,10} Women are likely to be more aware of their varicose veins and therefore are more likely to participate in studies leading to a selection bias. Also, age-adjusted prevalence of CVD in women has not been consistently performed in studies. In addition, pregnancy is a risk factor for CVD and is likely to bias the overall prevalence of CVD against women. Race has also been linked to CVD. In the San Diego Population Study, CVD was less prevalent in Blacks and Asians than in participants of European origin.¹¹ Another study showed that English women are five times at risk of CVD than Egyptian women.¹² Furthermore, other risk factors have been linked to CVD, and they include obesity,^{9,13} working in standing occupations,¹⁴ pregnancy,¹⁵ heredity,¹⁵ and prior history of limb trauma. In the Edinburgh Vein Study,⁹ participants with a family history of venous disease were more likely to develop varicose veins (odds ratio [OR], 1.75). Also in the same study, obesity was associated with an age-adjusted OR of 3.58 with the development

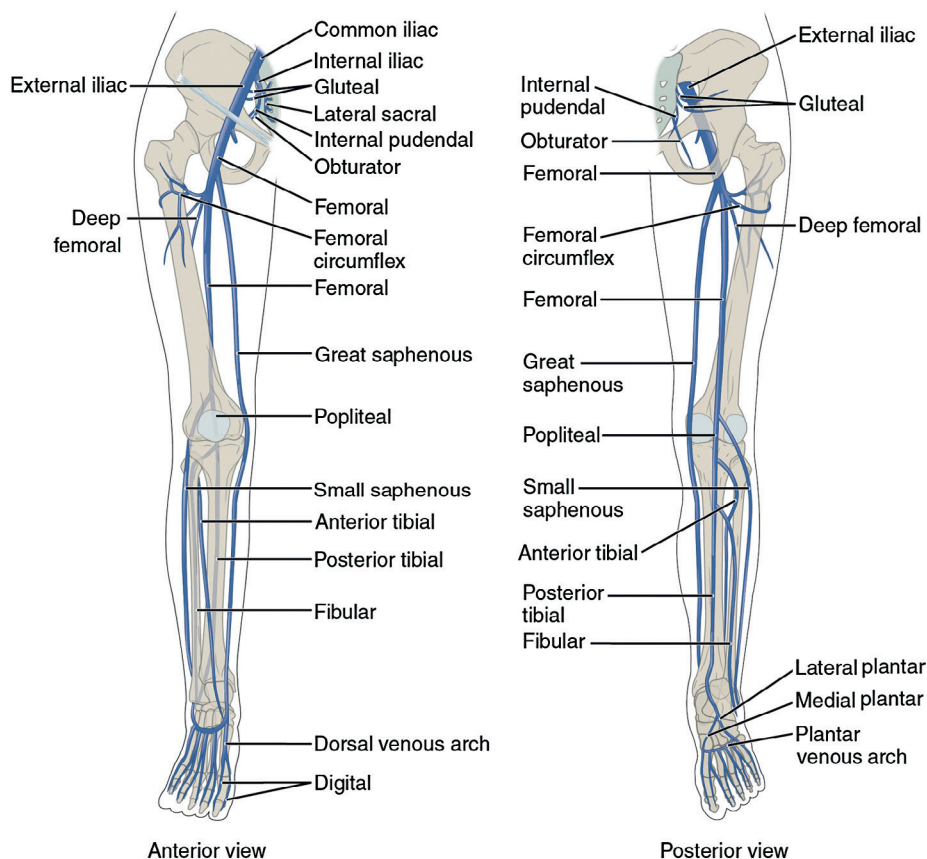


FIGURE 27.1 Anterior and posterior view of the major veins that drain the lower limb. (Reused with permission from OpenStax CNX. "Circulatory Pathways." Figure: Major veins serving the lower limbs. <http://cnx.org/content/m46646/latest/>.)

of CVI. In one study, obesity was also a risk factor for recanalization after endovenous thermal ablation, mostly noticeable in perforator veins.¹⁶ In another study,¹⁴ multivariate logistic regression analysis showed that female gender (OR, 2.2), increasing age (OR, 2.2–2.8), a reported positive family history for varicose veins (OR, 4.9), increasing number of births (OR, 1.2–2.8), standing posture at work (OR, 1.6), and higher weight (OR, 1.2) and height (OR, 1.4) were independent predictors of varicose veins.

Chronic venous insufficiency has a significant direct and indirect socioeconomic burden on society. In the United States, venous ulcerations resulted in a loss of 2 million workdays per year.¹⁷ In France and Sweden, 2.24 billion euros and 73 million euros were spent per year for the treatment of CVI, respectively.^{18,19} A study from Germany found that inpatient and outpatient direct costs were 250 million euros and 234 million euros, respectively; loss of working days costs were 270 million euros; and drug costs were 207 million euros.²⁰ The presence of venous ulcerations also had an impact on quality of life substantially with more than 20% of ulcers remained not healed within 2 years of follow-up.²¹ These ulcers have been responsible for early retirement of 12.5% of workers with this condition.²²

VENOUS ANATOMY AND PHYSIOLOGY

Treatment of patients with CVI requires a good understanding of normal venous anatomy and physiology. The veins of the lower limbs are divided into the superficial venous

system, the deep venous system, and the perforator veins, connecting the superficial and deep veins at various levels from the foot to the gluteal area (Figure 27.1). The superficial venous system is located within the superficial compartment surrounded anteriorly by the hyperechoic saphenous fascia and posteriorly by the muscular fascia. Within the saphenous compartment reside the saphenous veins, accompanying arteries, and saphenous nerves. A saphenous vein exiting the saphenous compartment is better described as a tributary. The superficial veins of the lower limbs are numerous and interconnected in a network that eventually empties into two primary trunks that feed into the deep venous system: the great saphenous vein (GSV) and the small saphenous vein (SSV). These superficial veins connect to the deep system at the level of the common femoral vein (CFV) for the GSV and quite often the popliteal vein (PV) for the SSV. Also, several perforators connect these superficial systems and their tributaries to the deep system. When discussing anatomy of the venous system, it is important to adhere to the current international nomenclature that has been adopted by the Union Internationale de Phlebologie and is currently in use.^{23,24} Discussed next is an anatomic description of the venous system of the lower limbs from this consensus meeting.

Superficial Veins of the Lower Limb

Great Saphenous Vein

The GSV is the longest and main superficial vein of the lower limb. It begins at the medial end of the arch as a



FIGURE 27.2 The great saphenous vein (GSV) located within the saphenous compartment. The “Egyptian eye” is seen. The superficial fascia is the upper eyelid, the deep fascia is the lower eyelid, and the lumen of the GSV is the iris.

continuation of the medial marginal vein of the foot. It ascends slightly anteriorly to the medial malleolus and continues anteromedially in the lower leg before it takes a short posterior course behind the medial condyle of the tibia at the level of the knee. In the lower thigh, it ascends anterolaterally, then takes a medial course to below the inguinal ligament, passing through the cribriform fascia that covers the fossa ovalis to join the CFV at the saphenofemoral junction (SFJ). The GSV is located within the saphenous compartment. The latter has been compared with the “Egyptian eye” when seen on transverse scan by B-mode ultrasonography (Figure 27.2). The superficial fascia is the upper eyelid, the deep fascia is the lower eyelid, and the lumen of the GSV is the iris. Outside the “eye,” the saphenous trunk is called a superficial tributary even though it can still play the role of a main axial superficial vein. There are several anatomic variations to the GSV; it can be a single GSV within the “eye” and no large tributary, rarely two parallel GSV within the same compartment (true duplication), or a single GSV in the proximal thigh and at various distances exit the “eye” to become a large subcutaneous tributary (present ~30% of the time). Large tributaries running parallel to the entire length of the GSV outside the saphenous compartment can also be present and enter the GSV at different levels.

There are several valves in the GSV ranging from 8 to 20 in number. They are mostly located at the junctions with other veins. A constant terminal valve in the GSV is located 1 to 2 mm distal to the SFJ. Often, a preterminal valve is seen 2 cm distal to the terminal valve and delineates the distal limit of the SFJ area. At the SFJ, a confluence of proximal veins is seen and includes the superficial epigastric vein, superficial circumflex iliac vein, and external pudendal vein (Figure 27.3). Their clinical importance is in their ability to transmit retrograde flow into the GSV despite a competent terminal valve. Also, the GSV receives many tributary veins; some may be large, including the anterior accessory saphenous vein (AASV) (present in 41% of participants and entering the GSV within 1 cm of the SFJ), and posterior accessory saphenous vein (PASV),

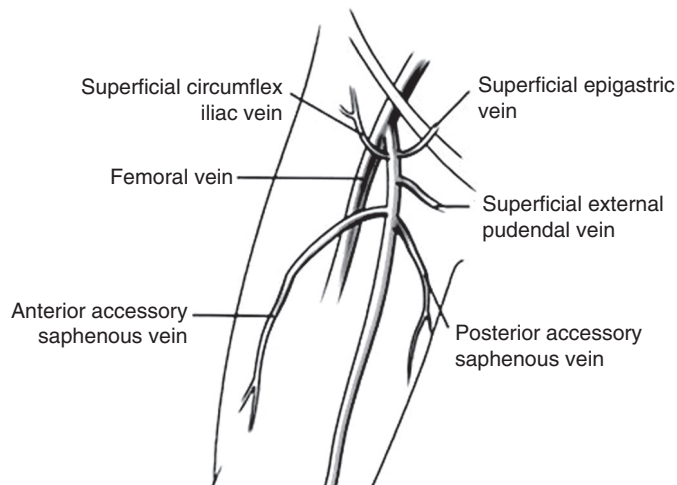


FIGURE 27.3 Proximal tributaries of the great saphenous vein.

often entering the GSV distal to the preterminal valve at variable distance. In addition, the anterior thigh circumflex vein ascends obliquely into the anterior thigh and enters either the GSV or the AASV; the posterior thigh circumflex vein ascends obliquely into the posterior thigh and may originate from the thigh extension (TE) of the SSV, directly from the SSV, or from the lateral vein plexus and enters the GSV. The lateral extension of the SSV into the thigh that connects with the posterior circumflex vein is often called the vein of Giacomini (Figure 27.4).

Anterior Accessory Saphenous Vein

The AASV enters laterally the GSV just below the SFJ. Close to the SFJ, both the AASV and GSV often share the same saphenous compartment. The AASV, however, has its own saphenous eye more distally and can be distinguished from the GSV by the “alignment” sign where it runs anterior and parallel to the GSV and in line with the femoral artery and femoral vein (FV). AASV reflux is commonly seen and carries similar morbidity to GSV reflux. It is also associated with a higher superficial vein thrombosis (6.41%) than GSV reflux (2.17%) ($P < .05$).²⁵

Posterior Accessory Saphenous Vein

The PASV ascends parallel and posterior to the GSV within its own fascial compartment. It is not always easily found, and it connects at various lengths with the GSV below the SFJ area. The PASV can be present above or below the knee. The below-the-knee segment that connects to the GSV is called Leonardo’s vein, or posterior arch vein, and is present in approximately 27% of individuals.

Small Saphenous Vein

The SSV is a continuation of the lateral marginal foot vein and ascends behind the lateral malleolus to the posterior aspect of the calf in between the medial and lateral heads of gastrocnemius muscle. The SSV lies within the interfascial compartment across its length. On transverse DU, the SSV appears within the “eye,” similar to the GSV. Proximally, it is within a triangular compartment outlined by the superficial fascia anteriorly and the lateral and medial heads of the

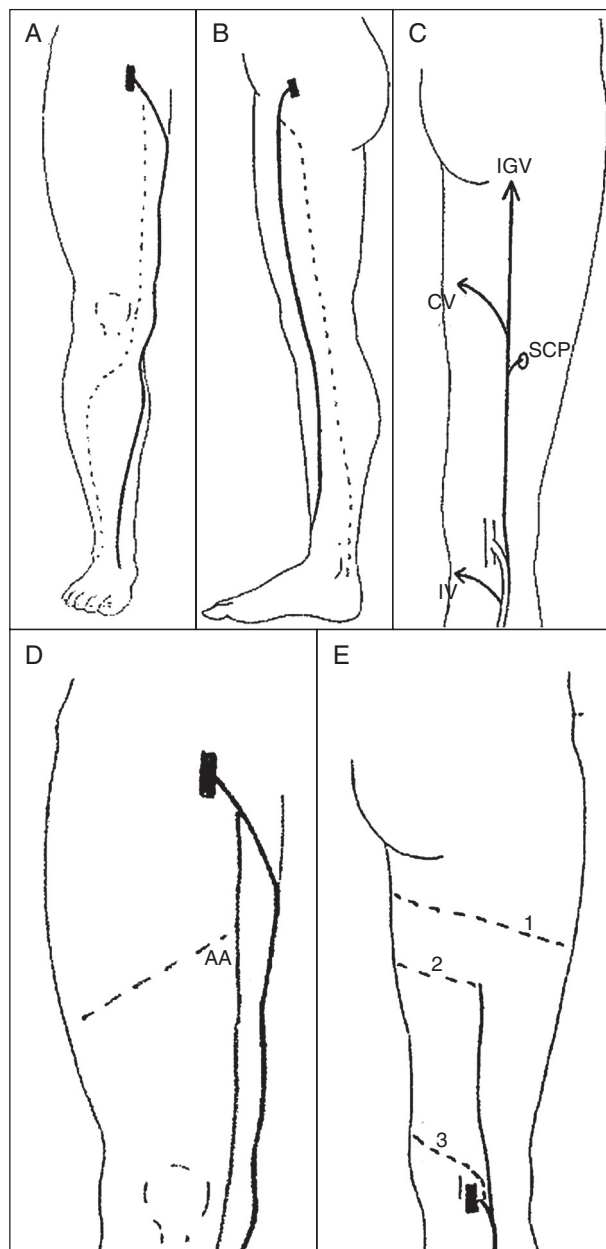


FIGURE 27.4 Course of the anterior accessory vein, posterior accessory vein, and thigh extension of the small saphenous vein. **A**, The course of the anterior accessory great saphenous vein (GSV; dotted line) is parallel and more anterior to the GSV (black line). **B**, The course of the posterior accessory GSV (dotted line) is parallel and more posterior with respect to the GSV (black line). **C**, The cranial extension of the small saphenous vein (black line) ends in the inferior gluteal vein (IGV) and can be connected to a sciatic perforator (ScP) or to the GSV via the posterior thigh circumflex vein (CV). One or more intersaphenous veins (IV) connect the small and GSVs at the calf. **D**, The anterior thigh circumflex vein (dashed line) ascends obliquely in the anterior thigh to reach the anterior accessory GSV (AA) or the GSV. **E**, The posterior thigh circumflex vein (dashed lines) originates from the lateral venous plexus (1), from the cranial extension of the small saphenous vein (2), or directly from the small saphenous vein (3). It courses obliquely in the posterior thigh toward the GSV. (Reused with permission from Caggiati A, Bergan J, Gloviczki, P, et al. Nomenclature of the veins of the lower limbs: an international interdisciplinary consensus statement. *J Vasc Surg.* 2002;36(2):416-422.)

gastrocnemius muscle laterally and medially, respectively. The SSV generally terminates in the PV at the saphenopopliteal junction (SPJ) but not always (Figure 27.5). The SPJ is mostly located within 2 to 4 cm above the knee crease, but this can significantly vary. The SSV continues into the thigh

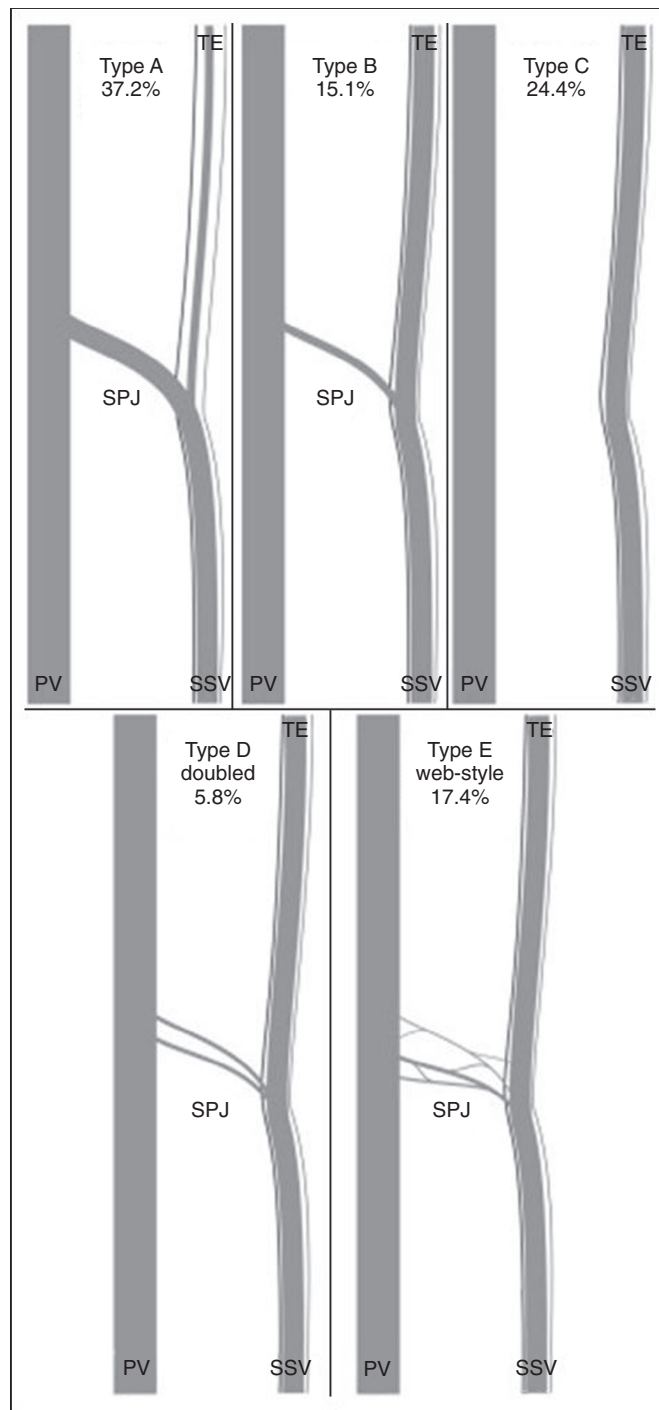


FIGURE 27.5 Anatomic variations of the small saphenous vein. Types A, B, C are labeled according to the UIP-consensus; type D represents a doubled saphenopopliteal junction (SPJ), and type E represents a web-style SPJ. PV, Popliteal vein; SSV, short saphenous vein; TE, thigh extension. (Reused with permission from Schweighofer G, Mühlberger D, Brenner E. The anatomy of the small saphenous vein: fascial and neural relations, saphenofermal junction, and valves. *J Vasc Surg.* 2010;51(4):982-989.)

as the TE. TE is present in 95% of participants and is intrafascial in position within a triangular compartment defined by the superficial fascia anteriorly, the semitendinous muscle medially, and the biceps femoris muscle laterally. The TE may end in the inferior gluteal vein, connected via a sciatic perforator or posterolateral thigh perforator to the FV, or connected to the GSV via the posterior thigh circumflex

vein. Both the TE of the SSV together with the posterior thigh circumflex vein that empties into the GSV are described as the vein of Giacomini. The gastrocnemius veins may merge with the SSV to empty into the PV, or they could empty directly into the PV near the SPJ. Like the GSV, there is a terminal valve in the SSV close to the PV, and a preterminal valve is generally located below the TE of the SSV.

Perforators of the Lower Limb

The superficial veins are connected to the deep veins via the perforator veins (Table 27.1) that penetrate the deep

TABLE 27.1 Perforator Groups and Subgroups in the Lower Limb

PERFORATOR GROUP	SUBGROUPS
Foot	Dorsal, plantar, lateral, medial
Ankle	Anterior, medial, and lateral
Leg	Medial: paratibial and posterior tibial (GSV or tributaries to PTV) Anterior: GSV tributaries to ATV Lateral: lateral venous plexus to peroneal Posterior: medial and lateral gastrocnemius, intergemellar (SSV to soleal) Para-Achilleal: SSV to peroneal
Knee	Medial, lateral, suprapatellar, infrapatellar, popliteal fossa
Thigh	Medial (femoral canal, inguinal), anterior, lateral, posterior (posteromedial, sciatic, posterolateral, pudendal)
Gluteal	Superior, mid, lower

ATV, Anterior tibialis vein; GSV, greater saphenous vein; PTV, posterior tibialis vein; SSV, small saphenous vein.

fascia. More than 40 perforator veins have been described. The perforators are located at several levels in the lower limb: foot, ankle, lower leg, knee, thigh, and gluteal area (Figure 27.6). From a historic point of view, they have been named after individuals who described them. Descriptive terms to their location are preferred and have been widely adopted, as follows:

- The perforators of the foot (*venae perforantes pedis*) are described into dorsal, medial, lateral, and plantar foot perforators.
- The ankle perforators (*venae perforantes tarsalis*) are the medial, anterior, and lateral ankle perforators.
- The perforators of the leg (*venae perforantes cruris*) are separated into four main groups:
 - Medial leg perforators (paratibial and posterior tibial). The paratibial perforators connect the GSV or its tributaries to the posterior tibial vein (PTV), and the posterior tibial perforators connect below the knee PASV to the PTV. These perforators are indicated by their location as upper, middle, and lower.
 - Anterior leg perforators connect the anterior tributaries of the GSV to the anterior tibial veins.
 - Lateral leg perforators connect veins of the lateral venous plexus to the peroneal veins.
 - Posterior leg perforators (medial gastrocnemius perforators, lateral gastrocnemius perforators, intergemellar perforators and para-Achilleal perforators connect the SSV to the soleal and peroneal veins.
- The perforators of the knee (*venae perforantes genus*) are designated as medial, lateral, suprapatellar, infrapatellar, and popliteal fossa knee perforators.

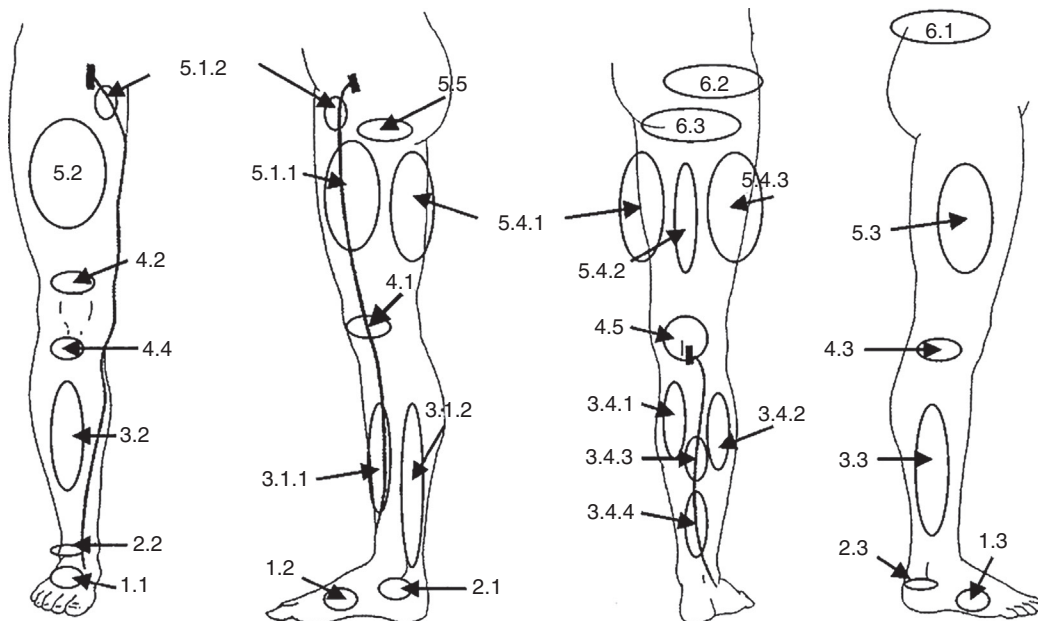


FIGURE 27.6 Main groups of popliteal vein. **Foot:** 1.1, dorsal foot; 1.2, medial foot; 1.3, lateral foot. **Ankle:** 2.1, medial ankle; 2.2, anterior ankle; 2.3, lateral ankle. **Leg:** 3.1.1, paratibial; 3.1.2, posterior tibial; 3.2, anterior leg; 3.3, lateral leg; 3.4.1, medial gastrocnemius; 3.4.2, lateral gastrocnemius; 3.4.3, intergemellar; 3.4.4, para-Achilleal. **Knee:** 4.1, medial knee; 4.2, suprapatellar; 4.3, lateral knee; 4.4, infrapatellar; 4.5, popliteal fossa. **Thigh:** 5.1.1, the femoral canal; 5.1.2, inguinal; 5.2, anterior thigh; 5.3, lateral thigh; 5.4.1, posteromedial thigh; 5.4.2, sciatic; 5.4.3, posterolateral thigh; 5.5, pudendal. **Gluteal:** 6.1, superior gluteal; 6.2, midgluteal; 6.3, lower gluteal. (Reused with permission from Caggiati A, Bergan J, Gliviczki P, et al. Nomenclature of the veins of the lower limbs: an international interdisciplinary consensus statement. *J Vasc Surg.* 2002;36(2):416-422.)

- The perforators of the thigh (venae perforantes femoris) are separated into the following:
 - Medial thigh (perforators of the femoral canal and inguinal perforators) connecting the GSV or its tributaries to the FV
 - Anterior thigh
 - Lateral thigh
 - Posterior thigh (posteromedial, sciatic perforators, posterolateral) and pudendal perforators
- The perforators of the gluteal muscles (venae perforantes glutealis) are divided in superior, mid, and lower perforators.

Deep Venous System

The deep venous system is located below the muscular fascia in the deep compartment. It is composed of axial veins and intramuscular veins. The deep venous system eventually receives all venous flow that empties in the right atrium. The main axial veins are the PV that becomes the FV above the knee when it passes through the adductor canal, then the CFV as it joins the deep femoral vein (DFV) at the groin level. The CFV leads to the iliac veins and then the inferior vena cava to the right atrium.

Intramuscular venous sinusoids coalesce and form the venous plexi within the soleal and gastrocnemius calf muscles. These gastrocnemius lateral and medial veins connect to form an extramuscular trunk that travels 1 to 4 cm into the popliteal fossa and empties directly into the PV, into the SSV at the level of the SPJ, or simultaneously into both popliteal and SSV. The soleus veins unite into one or several main trunks and terminate in either the PTV or the peroneal vein. The term *sural veins* refers to the lateral and medial gastrocnemius veins, soleal vein, and intergemellar vein; the latter courses deep to the SSV between the heads of the gastrocnemius muscles.

Physiology of the Venous System

The venous system functions as a large reservoir storing about 70% of the blood in the patient. It also serves as a low-flow, low-pressure conduit moving venous blood to the heart. Flow into the venous system travels against gravity; therefore, a series of muscle pumps and valves is built in to assist in this flow. Predominantly, calf muscle contraction and to a lesser extent foot and thigh muscles increase fascial compartment pressures, compressing the intramuscular veins and venous plexi in the calf and driving venous flow upward against gravity. Negative intrathoracic pressure also assists in the process of forward flow. A series of unidirectional bicuspid valves are present in the lower limb and superficial venous systems that continue to ensure a forward flow of blood to the heart against gravity.²⁶ Valves are also present at the perforators that prevent flow from the deep system back into the superficial system. The CFV typically has one valve. The inferior vena cava and common iliac veins have no valves. Infrequently, a valve can be seen in the external iliac vein. The infrainguinal veins have several valves located at different levels, but most seem to concentrate at the knee level and below.

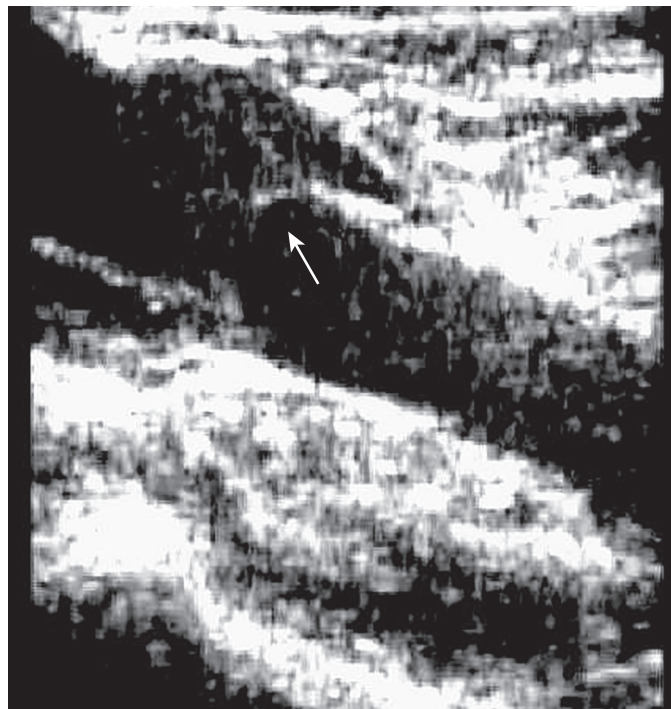


FIGURE 27.7 Venous valve (arrow).

The resting standing venous pressure is approximately 80 to 90 mm Hg. After ambulation, the muscle contraction moves the venous flow forward, emptying the venous system and dropping the pressure to 15 to 30 mm Hg. When muscle relaxation occurs, the venous system refills slowly (>20 seconds) from arterial inflow into the superficial and deep veins, distending the veins and allowing the valves (Figure 27.7) to open, creating a single pipe of fluid with a pressure at the ankle equal to the height of the column of blood. In a competent valve system, contraction of the muscle leads to quick emptying of the veins with no refluxing of flow backward and a quick drop of pressure in the venous system typically more than 50% decrease from the resting standing pressure.²⁷

ETIOLOGY AND PATHOPHYSIOLOGY OF CHRONIC VENOUS INSUFFICIENCY

The main pathophysiologic mechanism of CVI is high venous pressure in the lower extremity caused by failure in keeping venous upward flow toward the heart. This can result from backward reflux of venous flow through incompetent valves in the deep or superficial venous systems or the perforators that connect both. Venous obstruction in the deep system can also impede venous flow and contribute to high venous pressure. In addition, muscular dysfunction can contribute to reducing forward venous flow and along with reflux becomes an important risk factor for venous ulceration. When valve incompetence is present, the backward flow of blood to the lower veins contributes to raising the venous pressure faster to resting level (in <10–20 seconds). Also, the drop of venous pressure in an incompetent valve system with ambulation is blunted, and venous pressure remains higher than 50% its resting

value.²⁷ The constant high venous pressure in the lower limb is ultimately responsible for venous microangiopathy and subsequently the development of signs and symptoms of CVI.

Valve incompetence in the superficial veins may be caused by primary valve failure or weakness in the vessel wall. Secondary causes of valve incompetence can be trauma, hormonal effects, thrombophlebitis, or high pressure.²⁸ There are several potential sources of reflux from the deep system into the superficial system via incompetent perforators, SPJ, or SFJ. Also, reflux can be transmitted from the GSV, perineal veins, and thigh perforators to the SSV via the Giacomini vein, backward from the SPJ to the GSV, or from the veins of the posterior aspect of the thigh via the same system.²³ The deep system could also develop significant reflux mostly caused by obstruction, partial or complete. This can be related to deep vein thrombosis (DVT), stenosis, or extrinsic compression. Compression of the iliac vessels can produce obstruction to upward venous flow resulting in high venous pressure, leading to vein dilation and reflux. Iliac extrinsic compression is quite often an underestimated cause of CVD, and a high index of suspicion is needed to correctly identify this problem.²⁹ Finally, muscle pump dysfunction is a contributor to venous ulcerations in patients with venous reflux. Reflux in conjunction with muscle pump failure is a significant risk factor for developing venous ulcers. The presence of good muscle pump function lessens the chance of ulcerations in patients with severe reflux, and the presence of poor muscle function can increase the risk of ulceration, even when minimal reflux is present.^{30,31}

Venous microangiopathy is the result of high venous pressure transmitted to the microvasculature of the lower legs. In its mild form, CVI results in an increase in transcapillary diffusion of sodium fluorescein (NaF), a marker of leak in the capillary bed seen early in the disease process, and is accompanied by an increase in pericapillary space (halo). As CVI progresses and becomes more severe, capillary thromboses occur, leading to a reduced capillary density and a reduction in transcutaneous oxygen tension (tcpO_2), particularly at the ulcer rim. The remaining capillaries become more elongated and tortuous. They become more permeable because of the stretching of their interendothelial pores. Larger molecules can exit the capillaries into the extracapillary space, leading to chronic inflammation and edema and eventually skin trophic changes and ulcerations. Also, in the severe stages of CVI, there are a destruction of the lymphatic capillary network and an increase in the permeability of the remaining lymphatic fragments, suggesting lymphatic microangiopathy.³² Dysfunction of local nerve fibers also occurs.

There are several hypotheses on how microangiopathy leads to venous ulcerations. Browse and Burnand³³ proposed the fibrin cuff theory, which centers on the leak of fibrinogen into the pericapillary space. This results in pericapillary fibrin cuffs that were thought to be a barrier for diffusion of oxygen. Fibrin cuffs, however, are not a specific finding for venous ulceration and were found not to impair oxygen diffusion significantly.³² Another theory is the trapping of leukocytes in the capillaries or postcapillary venules with subsequent release of their inflammatory

mediators and proteolytic enzymes, leading to endothelial injury.³⁴ Finally, trapping of leaked growth factors in the pericapillary space is thought to prevent their ability to participate in the healing of damaged capillary bed.³⁵

EVALUATION AND CLASSIFICATION OF PATIENTS WITH CHRONIC VENOUS INSUFFICIENCY

Chronic venous disease presents with a spectrum of pathologies ranging from telangiectasia to skin hyperpigmentation to venous ulcers. The term CVI is generally used for patients with an advanced form of CVD generally presenting with symptoms and signs of lower extremity edema, trophic skin changes, and venous ulcerations.

The initial evaluation of a patient with CVI starts with a comprehensive history and physical examination.³⁶ Symptoms of CVI include heaviness, achiness, tightness, itching, muscle cramps, involuntary movements of the limb, and tingling. These worsen when patients are standing and improve when the feet are elevated at heart level. Patients' symptoms are worse as the day progresses, and generally mild or fewer symptoms are noted in the morning before standing when getting out of bed. The interference of symptoms with daily activity and the response to prior treatment such as compression garments should be documented. Risk factors for developing CVD should be identified, such as advanced age, a higher weight and height, standing occupation, heredity, prior injury, surgeries or trauma, history of DVT, multiple pregnancies, and ethnic background. A past history of early childhood varicose veins is important to note because it may be related to some rare congenital blood vessel malformations such as in Klippel-Trénaunay-Weber syndrome.³⁷ Providers need to keep in mind other sources of pain that may mimic CVI, including tendinitis, arthritis, neuropathy, and arterial insufficiency. Careful history and examination should help in identifying these causes.

The physical examination should be performed in a warm, well-lit room and when the patient is standing. The entire leg needs to be checked starting from the inguinal area to the foot, and findings of abnormal veins, skin changes, or ulcerations need to be well documented on a drawing showing the anterior, posterior, medial, and lateral parts of the leg. Palpation over the GSV, SSV, SFJ, and SPJ may reveal additional varicosities, subcutaneous cords, or areas of indurations not visible with inspection only. Palpation of the SFJ with cough can reveal a thrill that indicates reflux at this level (cough impulse test). Also, a tap on the GSV distally while palpating the SFJ area may allow the feeling of a transmitted pulse to the SFJ, indicating GSV distension. The opposite is true with a tap on the SFJ, allowing a feeling of transmitted pulse to the distal GSV indicating reflux (the tap test).³⁸ These tests, however, lack good sensitivity in identifying reflux at the SFJ. The Brodie-Trendelenburg test can help identify perforator reflux into the GSV. The patient's leg is elevated 45 degrees, and blood is massaged up the leg from the foot. A tourniquet is then applied proximally close to the groin area. The patient is then allowed to stand up. If no dilation of the

lower leg veins is seen after 20 to 30 seconds, perforator valves are likely to be competent. If after releasing the tourniquet, the veins in the leg distend quickly, this indicates that the superficial venous system is incompetent. This test is highly sensitive but poorly specific in identifying superficial and perforator reflux.³⁸ Another test that can be performed in the office is the Perthes test. A tourniquet is placed below the knee in a standing position. The patient is asked to raise the heel 10 times. If varicosities empty, this indicates that the perforators of the lower superficial venous system are competent, and reflux is likely cranial to the tourniquet. On the other hand, if more distension occurs to the varicosities of the lower leg, this indicates that reflux is present in the deep perforators below the knee. The presence of severe pain in the calf with raising the heel repetitively could indicate the presence of DVT. These physical maneuvers have been widely replaced with DU to the lower leg, which has higher accuracy in identifying the presence and location of the reflux.

After the examination and history are obtained, disease needs to be classified based on its clinical presentation. The Clinical, Etiologic, Anatomic, and Pathophysiologic (CEAP) classification system was developed at the American Venous Forum annual meeting in 1994 and revised in 2004.³⁶ Updated CEAP 2020 guidelines recently focused on recurrent varicosities and recurrent ulcers as well as the presence of corona phlebectatica.³⁹ The physical findings are divided into seven clinical manifestations ranging from no visible findings of CVD to active venous ulcerations. Given the progression of CVD, the classification also reflects the natural clinical progression of this disease. The etiologic, anatomic, and pathophysiologic classifications require additional anatomic and functional testing that will be discussed later. The CEAP classification is described in Table 27.2, and clinical manifestations are shown in Figures 27.8 to 27.11.

The venous clinical severity score (VCSS)⁴⁰ (Table 27.3) was designed to complement the CEAP score and to provide a method to serially assess the severity of disease over time and in response to a treatment. The advantage

TABLE 27.2 Clinical Manifestations Classes Per Clinical, Etiologic, Anatomic, and Pathophysiologic Classification

GRADE	DESCRIPTION
C0	No visible or palpable signs of venous disease
C1	Superficial telangiectasias (intradermal, <1 mm, flat, red vessels) or reticular veins (subdermal, 1–3 mm, flat, bluish) or venulectasias (rise above skin, 1–2 mm, blue)
C2	Varicose veins (diameter $\geq$ 3 mm)
C2r	Recurrent varicose veins
C3	Ankle edema
C4	Changes in skin and subcutaneous tissue
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C4c	Corona phlebectatica
C5	Healed venous ulcer
C6	Active venous ulcer
C6r	Recurrent active venous ulcer



FIGURE 27.8 Clinical, Etiologic, Anatomic, and Pathophysiologic class I with telangiectasias (spider veins).



FIGURE 27.9 Clinical, Etiologic, Anatomic, and Pathophysiologic class II with large varicosities.



FIGURE 27.10 Clinical, Etiologic, Anatomic, and Pathophysiologic class IVb with skin hyperpigmentation and atrophie blanche changes.



FIGURE 27.11 Clinical, Etiologic, Anatomic, and Pathophysiologic class VI with a nonhealing venous ulcer.

of the VCSS is that it is dynamic and is able to capture changes in disease severity, whereas the CEAP class is descriptive and static, particularly in its advanced classes (IV–VI).

The venous severity score (VSS) is another scoring system that grades disease severity and is sum score of multiple other scoring systems, including the VCSS, Venous Segmental Disease Score (VSDS), and Venous Disability Score (VDS).⁴¹ Other scoring systems are present, and one should adopt a scoring system that complements the CEAP score to be able to assess longitudinal changes in patients' symptoms and signs of CVI either naturally or after intervention.

ANATOMIC AND PHYSIOLOGIC TESTING OF CHRONIC VENOUS INSUFFICIENCY

Several anatomic and physiologic tests can be used to diagnose and understand the cause of CVI. The most practical and commonly used test in an office setting is DU and to a lesser extent plethysmography.

Duplex Venous Ultrasonography of the Lower Limb

Duplex venous ultrasonography is likely to be the most widely used technique in the diagnosis of venous disorders, including DVT and superficial venous disease. This section focuses on the use of DU in the diagnosis and management of patients with chronic superficial venous disease. An evaluation of the deep venous system is routinely performed when assessing superficial venous reflux to rule out coexistent DVT, assess for deep venous reflux, and assist in the diagnosis of potential iliac obstructive disease.⁴²

Spectral Doppler flow is used to determine the degree of reflux in the superficial venous and deep venous systems (Figure 27.12). Reflux in the deep venous system is evaluated in the supine position with the head elevated 10 to 15 degrees. Evaluation of the superficial venous system needs to be performed with the patient in the standing position with distal augmentation and standing with the weight mostly on the contralateral leg. The heel of the leg under examination should be flat on the floor to avoid calf muscle contraction during the test. The cutoff for abnormal retrograde flows are greater than 500 ms in the superficial system and deep calf veins but greater than 1000 ms in the femoropopliteal vein. Reflux in the perforator vein is abnormal if it is more than 350 ms,⁴³ but the cutoff for clinical intervention is more than 500 ms. Reflux is best reported in seconds rather than graded in severity as mild, moderate, or severe because the correlation with the severity of disease is not standardized and is variable. Initially, the SSV is interrogated, including its relationship to the PV. The TE of the SSV will also need to be identified along with its termination. Next, the GSV and its tributaries are evaluated. In approximately 2% of the time, there is a duplicate GSV.⁴⁴ Reflux and GSV sizes are measured at the level of the SFJ, midthigh, and above and below the knee. Mapping the AASV and the PASV follows the GSV. Furthermore, tributaries at least 50% the size of the native saphenous veins are mapped.⁴⁵ Finally, perforators' veins

TABLE 27.3 Venous Clinical Severity Score

ATTRIBUTE	ABSENT = 0	MILD = 1	MODERATE = 2	SEVERE = 3
Pain	None	Occasional pain or other discomfort	Daily pain or other discomfort	Daily pain or discomfort that limits most regular daily activities
Varicose veins ≥ 3 mm in diameter	None	Scattered; includes corona phlebectatica	Confined to calf or thigh	Involves calf and thigh
Edema	None	Limited to foot and ankle	Extends above ankle but below knee	Extends to knee and above knee
Pigmentation	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Above lower third of calf
Inflammation	None	Limited to perimalleolar area	Diffuse over lower third of calf	Above lower third of calf
Induration	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Number of active ulcers	0	1	2	≥ 3
Duration of longest active ulcer	None	<3 mo	>3 mo but <1 y	Not healed for >1 y
Size of largest active ulcer	None	Diameter <2 cm	Diameter 2–6 cm	Diameter >6 cm
Compression therapy	Not used	Intermittent use of stockings	Wears stockings most days	Full compliance: stockings

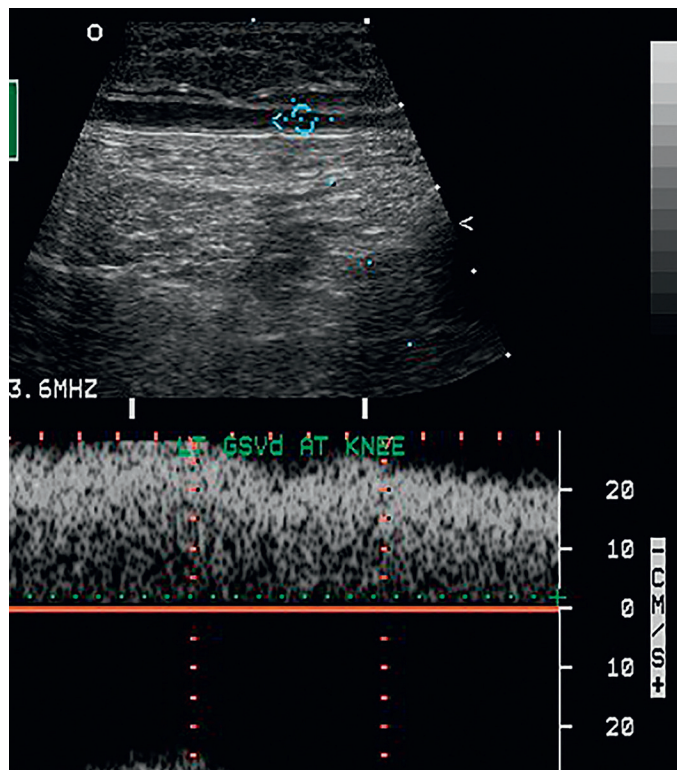


FIGURE 27.12 Spectral Doppler showing reflux in the great saphenous vein.

are mapped, which is particularly important in patients with healed and nonhealed venous ulcerations. An extensive mapping of perforators is less useful. Perforators large enough to be larger than 3.5 mm in diameter and with reflux more than 500 ms are of particular importance in patients with venous ulcerations because these perforators are typically the target for therapeutic intervention. The mapping data are then compiled into a diagram that is used for diagnostic and therapeutic intervention.

Duplex ultrasonography can also identify other pathologies, including aneurysms, tumors, or the presence of Baker's cyst in the popliteal fossa. In addition, it helps monitor the success of endovenous ablative procedures and in the progression of reflux in symptomatic patients. Guidelines of the American Venous Forum on DU scanning in patients with venous reflux indicate that DU is recommended as the first diagnostic test for all patients with suspected CVI. DU is also indicated for follow-up after successful endovenous ablation procedure if symptoms have recurred. Routine application of DU, however, after successful ablation and with no symptoms' recurrence is not indicated.

Plethysmography

Plethysmography provides functional information that is complementary to DU in the management of CVI.^{46,47} Plethysmography is a test that quantitatively measures blood volume changes within the leg. Air plethysmography (AP) is a convenient and inexpensive test that uses an air-filled long cuff to measure fluctuations in leg volume. In AP, the patient starts in a supine position. The leg being examined

is raised up at 45 degrees for 5 minutes to cause venous emptying. An air-filled cuff is then placed below the knee and inflated at 6 mm Hg. The patient is then placed in the standing position, and the leg veins are allowed to fill via arterial influx and venous reflux. Maximum venous volume (VV) (in milliliters) is then recorded. The time to fill 90% of the VV is determined (VFT90) (in seconds). A venous filling index (VFI) is then calculated ($VV/VFT90$ [in milliliters per second]). The patient is then asked to flex the ankle to contract the calf muscle. The volume of blood ejected is recorded (EV). The ejection fraction (EF) of the calf muscle contraction is then calculated ($EF = EV/VV \times 100$). After the VV is restored, 10 consecutive tip-toe movements are done. Residual volume (RV) is determined from time zero. Residual volume fraction (RVF) is then calculated using the formula $RV/VV \times 100$ (Figure 27.13).

The VFI correlates with the clinical severity of CVI through class 2 of the CEAP classification.^{48,49} Clinical deterioration beyond class 2 does not correlate with further deterioration of hemodynamics. VFI greater than 5 mL/s correlates with deep venous and perforator reflux,⁴⁷ and greater than 7 mL/s identifies the risk of "critical" deep venous reflux likely to be predictive of venous ulceration.⁵⁰ VFI is also a predictor of multisystem reflux (deep, superficial, and perforator).⁵¹ VFI of 6.68 mL/s correlated with triple-system incompetence, whereas a VFI of 4.5 mL/s correlates with a dual-system incompetence. The number of incompetent system increases with clinical severity of disease. In general, however, all AP parameters are poor predictors for severe disease or ulcerations.⁴⁷ EF and RVF are good indicators of calf muscle function, but they rarely influence the clinical severity of disease and do not discriminate between different types of reflux.⁴⁷

TREATMENT OF SUPERFICIAL CHRONIC VENOUS INSUFFICIENCY

Chronic venous insufficiency is a progressive disease.⁵² Treatment of all sources of reflux is important to reduce symptoms and obtain a successful outcome. In a retrospective study of 263 patients, ablation of tributaries of the superficial venous pathways in the same setting of GSV reflux treatment reduced the rate of recurrence of superficial venous reflux disease and improved symptoms.⁵³ Initially, it was thought that reflux is always descending, starting at the level of the CFV or the SFJ and progressing distally. Several studies, however, indicate that vessel wall changes may occur at any level, causing segmental reflux with no junctional or proximal reflux.^{54,55} In fact, reflux develops in most people at the knee or the calf level with no involvement of the saphenous junctions.⁵⁶ Patients younger than 30 years of age have several refluxing tributaries of saphenous or nonsaphenous veins and statistically less involvement of the junctions compared with patients older than the age of 60 years. In this study, 44% of varicose limbs also had a normal saphenous vein.⁵⁷ In addition, retrograde reflux is seen from the vein of Giacomini into the GSV, leading to GSV reflux with no SFJ involvement. Finally, refluxing perforators into the superficial veins may occur, leading to segmental saphenous reflux.

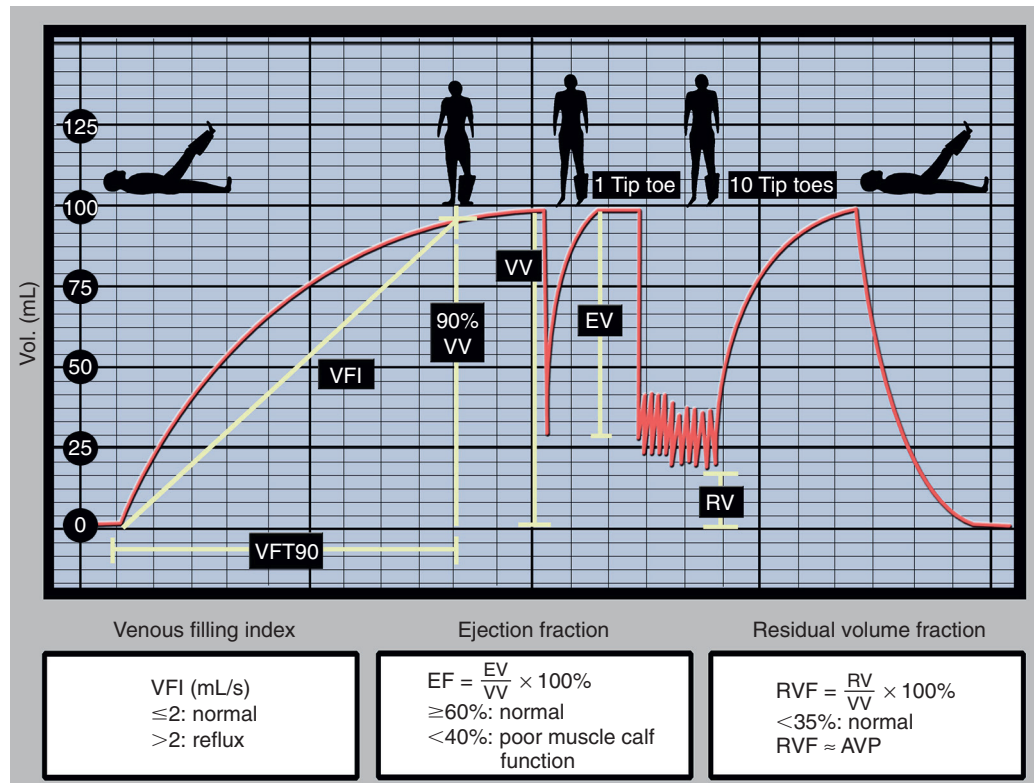


FIGURE 27.13 Air plethysmogram. The venous filling index (VFI) = $VV/VFT90$ (in milliliters per second). The ejection fraction (EF) of the calf muscle contraction is = $EV/VV \times 100$. Residual volume fraction (RVF) is = $RV/VV \times 100$. AVP, Air Venous Plethysmography; EV, volume of blood ejected; RV, residual volume; VFT90, time to fill 90% of the VV (per second); VV, venous volume. (Reused with permission from *J Physiol.* 1986, 374(suppl):11P, figure 1B, Wileyonline Publication.)

Superficial venous reflux quite often coexists with deep venous reflux. Segmental deep venous reflux can be induced by reflux from incompetent veins draining into the deep system.^{58,59} In one study, ablation of incompetent superficial venous reflux eliminated coexistent incompetence in the deep venous system in 94% of patients.⁶⁰ Also, complete GSV surgical stripping significantly reduced deep venous reflux on postoperative DU, whereas incomplete stripping of refluxing GSV was associated with the development of new deep vein reflux on follow-up.⁶⁰ Finally, in a recent study, 154 patients (223 limbs) who underwent RFA of the GSV were retrospectively analyzed. At 1-month follow-up, the functional VV and VFI were significantly decreased in postoperative values than in preoperative values ($P < .001$). Also, the number of limbs with deep venous reflux significantly decreased postoperatively than preoperatively ($P < .001$). Furthermore, there were significant differences in CFV and PV after GSV treatment ($P < .001$).⁶¹

When significant swelling in the lower legs or ulcerations cannot be explained by the degree of reflux seen in the superficial veins, iliac venous compression needs to be ruled out. Furthermore, in case of unilateral swelling with combined deep and superficial venous reflux, DVT and pelvic venous compression syndrome need to be ruled out before superficial venous ablation (Figure 27.14 and Videos 27.1 and 27.2). The presence of DVT with no axial flow in the femoropopliteal vein or severe iliac compression should be considered a contraindication to ablate the superficial vein. Finally, venous claudication, particularly

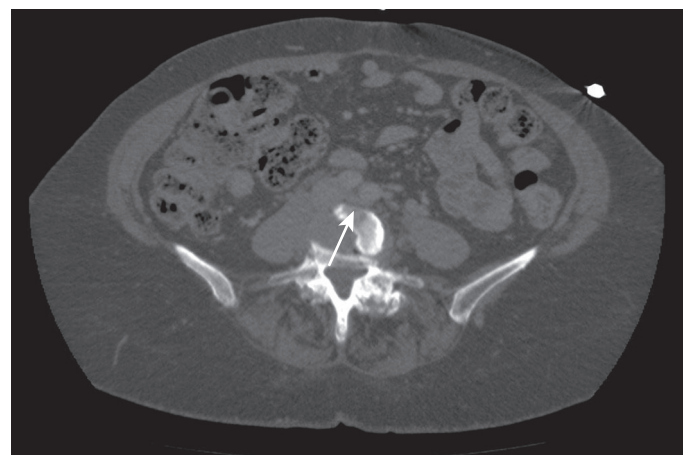


FIGURE 27.14 Left common iliac vein compression by the right iliac artery consistent with May-Thurner syndrome.

with an increase in venous pressure by three times the normal with exercise compared with the contralateral leg, should raise suspicion for an iliac compression syndrome.⁶² A decrease in phasicity at the level of the CFV in the affected leg compared with the contralateral CFV should raise suspicion for a venous compression syndrome.⁶³ Computed tomography with venous filling phase (CTV) or magnetic resonance venography (MRV) may confirm the diagnosis. The most reliable test, however, in identifying iliac venous compression is the intravascular ultrasonography.

The treatment of patients with superficial venous reflux can range from graded compression therapy, which is generally the first-line treatment, followed by ablative or surgical stripping of the refluxing superficial veins if symptoms persist. Later in this chapter is a description of various therapies for superficial venous reflux and CVI.

Compression Therapy

Compression therapy is effective in reducing the symptoms of discomfort, swelling, and ulcerations in patients with CVI. Historically, this method of treatment has been used since antiquity⁶⁴ and remains the standard of care in the initial treatment of patients with venous insufficiency. Its aim is to reduce capacity and pressure within the venous system of the lower limbs, reduce edema by accelerating venous return, and aid in venous ulceration healing. This can be achieved with bandages, compression stockings, or dynamic intermittent compression. Compression therapy is indicated for all classes of the CEAP grading system and for patients with lymphedema. Also, quite often, compression therapy is used for DVT prophylaxis and for post-DVT management to reduce postthrombotic syndrome.⁶⁵

Before initiating compression therapy, patients need to be ruled out for severe peripheral arterial disease. An ankle-brachial index (ABI) of less than 0.5 should be considered a contraindication to compression bandages or stockings. A reduced compression pressure needs to be considered for patients with moderate reduction in their ABI (0.5 to 0.7).⁶⁶ Also, there is no contraindication to use moderate compression pressure in patients with diabetes mellitus and venous ulcerations. In 155 patients, the median healing times were 27 weeks for patients without diabetes and 29 weeks for patients with diabetes ($P = -0.19$) with venous ulcers and moderate compression pressure.⁶⁷ Compression pressures are classified into mild (<20 mm Hg), moderate (20 to <40 mm Hg), strong (40 to <60 mm Hg), and very strong (≥ 60 mm Hg).⁶⁸ The worse the symptoms, the higher the pressure needed. Typically, strong (>40 mm Hg) compression is used for patients with venous ulcerations when tolerated and with no contraindication. There has been some debate, however, about the optimal pressure needed to achieve the desired clinical outcome in patients with leg discomfort and edema. A meta-analysis of randomized controlled trials comparing stockings with ankle pressure of 10 to 20 mm Hg versus more than 20 mm Hg showed no added benefit of the higher pressure versus the lower pressure in these categories. Pressure less than 10 mm Hg was ineffective in alleviating symptoms.⁶⁹ Recently, the concept of upward progressive compression was introduced. Compression stockings can be upward progressive (pressure highest at calf) or degressive (pressure highest at the ankle). In one randomized trial, upward progressive compression was more effective at 3 months in improving pain or heaviness in the legs without the development of DVT or ulcerations.⁷⁰

Compression therapy, whether using bandages or stockings, can be elastic (high pressure at rest, less pressure with muscle contraction) or rigid or inelastic (low pressure at rest, high pressure with muscle contraction). In addition, it can be single or multilayered. If multilayered, it

can be a combination of elastic and inelastic support. In general, bandages are used during the active phase of treatment (lymphedema, ulcerations, excessive swelling) or in patients who cannot tolerate or are not capable of applying compression stockings. The pressure applied by the bandages is variable and operator dependent. Compression stockings provide reliable pressure and are generally applied for prevention of symptoms and edema or to prevent progression of disease to ulceration. Comparative effectiveness data between below-the-knee and above-the-knee compression stockings are lacking. In addition to static compression, dynamic compression has been used along with manual lymphatic drainage to treat primary and secondary lymphedema.⁶⁴ Dynamic compression uses sequential inflation and deflation to enhance venous return and improve edema. They are effective in patients who cannot tolerate stockings or bandages or have limited muscular function or severe arterial disease.⁶⁸

Endovascular Heat Ablative Therapies

Endovascular ablative therapies consist of thermal and nonthermal ablation methods. Thermal (or endovascular heat ablation [EVHA]) is a highly effective technique in ablating refluxing saphenous veins. It is an office-based procedure with minimal complications and a quick recovery for the patient. EVHA has largely replaced surgical stripping. It consists of either endovascular laser ablation (EVLA) or endovascular radiofrequency ablation (EVRA). Steam ablation is also a thermal ablative method available in Europe but not yet approved in the United States.

Endovascular Laser Ablation

Endovascular laser ablation exerts its action via thermal injury to the vessel wall, the mechanism of which is still not very well defined.⁷¹ Current lasers use a continuous energy delivery system instead of the pulsed method of the older generation. The extent of transmitted energy from the laser (Figure 27.15) to the vessel wall depends on several factors. Some of these factors include the power

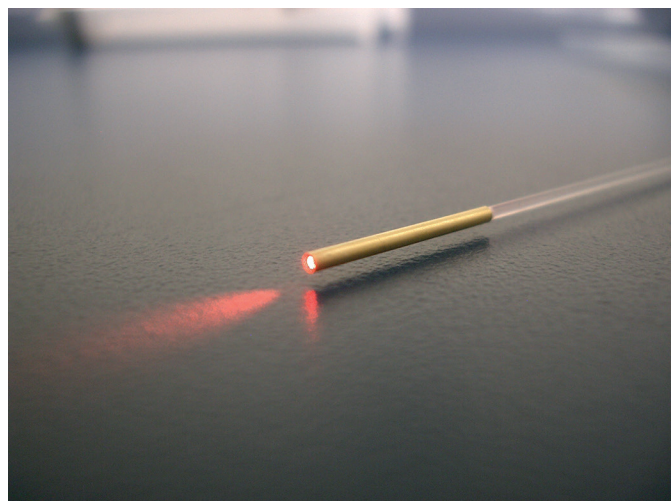


FIGURE 27.15 Laser energy seen at the tip of the NeverTouch gold-tip fiber. (Courtesy of AngioDynamics.)

settings (watts or joules per seconds), velocity of pullback of the laser fiber (cm per seconds), and vessel diameter. Other factors may include the wavelength of the laser, fiber contact with vessel wall, and the type of fibers used (covered versus noncovered), but these need to be more validated in controlled studies. Frequently, the linear endovenous energy density (LEED, in joules per centimeter) is reported with laser ablative therapy and is essentially a reflection of the amount of energy released per cm of vessel treated. The LEED is derived from the laser power and the velocity of pullback of the fiber (laser power/velocity of pullback = LEED). Therefore, a low energy at low pullback speed may result in the same LEED as a high energy at high pullback velocity. For unified reporting in the case of continuous energy lasers, reporting the LEED alone without reporting the speed of pullback or the laser power would render comparative conclusions among different lasers potentially misleading.^{72,73}

The energy transfer of the laser is generally to either the red blood cells or water in the vessel wall depending on the laser wavelength. Vessel wall water has a higher affinity to higher wavelength lasers (1319, 1320, and 1470 nm), whereas red blood cells have a higher affinity to shorter wavelength lasers (810, 940, and 980 nm). Energy can be transmitted by direct vessel contact with the laser hot tip (using older generation pulsed lasers with bare fibers and a common cause of perforation), boiling steam bubbles mediated by red blood cells with shorter wavelength lasers, and heat conduction.⁷³ It is speculated that higher wavelength lasers with covered tip fibers have the ability to generate the desired LEED with less power and less direct contact with the vessel wall; therefore, they have less ecchymosis and discomfort.^{74,75} The importance of the wavelength needs to be further validated. However, using the same LEED and power, one study suggested that the 1320-nm laser had less ecchymosis and pain on follow-up than the 810-nm laser.⁷⁶ It is speculated that whereas higher wavelength lasers are likely to cause heat-induced vessel wall damage by fibrosis and scarring, the shorter wavelength lasers cause red blood cell destruction and thrombosis. Current studies indicate that the optimal LEED needed for effective ablation is between 60 and 100 J/cm for effective ablation.⁷⁷⁻⁷⁹ A retrospective study of 287 patients treated for CVI with the 1470-nm diode laser showed a 94.4% occlusion rate of the GSV with an average LEED of 45.90 J/cm and 96.4% in the SSV with an average LEED of 44.07 J/cm.⁸⁰ In some studies, however, lower LEEDs (20–30 J/cm) have been reported to be effective with the 1470-nm laser.⁷⁴

Compared with surgical ligation and stripping, abolishment of reflux and improvement in quality of life were similar with the laser with more postoperative hematomas seen with surgery and more bruises with the laser. In the same study, a slightly higher reopening of GSV is seen with the laser compared with surgery at 2 years.⁸¹

Endovascular Radiofrequency Ablation

Radiofrequency ablation (RFA), also called Venefit Targeted Endovenous Therapy (formerly known as the VNUS Closure procedure), is performed using the Covidien ClosureFast catheter (Covidien), inserted under tumescent

local anesthetic into the GSV or SSV. The RF energy causes thermal injury to the vein wall and results in vessel wall inflammation, fibrosis, and closure. The mechanism by which RFA generates heat is resistive to the tissue that is in direct contact with the electrode. Heat is then conducted to deeper tissue, causing endothelial denudation, denaturation of collagen, and obliteration of the vein with a fibrotic seal. Minimal thrombus or coagulum is formed.⁸²

Radiofrequency ablation is very effective in closure of the GSV, SSV, or perforators. It compares favorably with surgical ablation with less pain, and a faster recovery as was shown in the Prospective Randomised Study of Endovenous Radiofrequency Obliteration (Closure) Versus Ligation and Vein Stripping (EVOLVEs). In this study and at 2-year follow-up, RF closure of GSV was statistically similar to surgical ligation and stripping with the majority of GSV remained closed, and 41% became undetectable because of progressive shrinkage.⁸³ Compared with EVLA, EVRA has less ecchymosis and pain in the first 2 to 3 weeks after the treatment, which is particularly true for the early laser generation. A recent study,⁸⁴ however, continued to show less postoperative discomfort and faster return to work and normal activities with RFA compared with EVLA in a patient population randomized predominantly to the 1470-nm laser versus RFA. Irrespective, both treatment modalities were effective at 1 year with only 5.8% and 4.8% of GSV patent with the laser and the radiofrequency modalities, respectively.⁸⁴

Complications of RF ablation include discomfort, vagal reaction, dysrhythmia, saphenous nerve pain, paresthesia, skin burn, hematoma, thrombophlebitis, DVT (<1%),⁸⁵ and infection. Paresthesia is usually mild and transient but can occur in 2% to 23% of patients. Endovenous heat-induced thrombosis (EHIT) (Figure 27.16) involving the SFJ and SPJ is rarely associated with pulmonary embolization. An increasing ablation distance peripheral to the SFJ (from 2 to 2.5 cm) could result in a reduced rate of EHIT.⁸⁶ Other risk factors for EHIT include thrombophilia, use of anesthesia with delayed ambulation postprocedure, and poor ablation

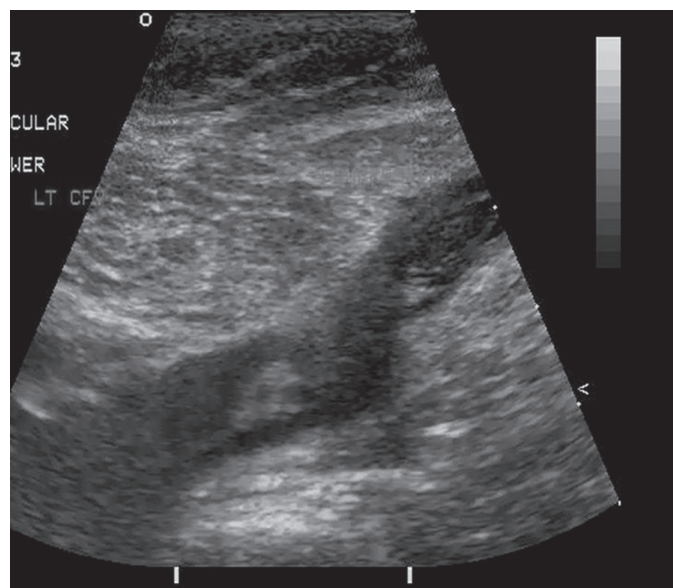


FIGURE 27.16 Heat-induced thrombosis extending into the deep system from the great saphenous vein.

technique. A recent study also showed that a classification of C3 or greater (OR, 3.39; 95% confidence interval [CI], 1.30–8.86; $P = .013$), GSV greater than 7.5 mm (OR, 3.32; 95% CI, 1.33–8.25; $P = .010$), and short superior epigastric vein to SFJ distance (OR, 2.71; 95% CI, 1.09–6.71; $P = .032$) are also risk factors for EHIT.⁸⁷ A recent review of 52 studies (16,398 patients) showed that thrombotic complications are infrequent. Type 2, 3, or 4 EHIT occurred in 1.4% of cases, DVT in 0.3% of cases, and pulmonary embolism (PE) in 0.1% of cases with similar results in both RFA or laser endovascular therapies.⁸⁸ Typically, thrombi not extending into the deep system are treated conservatively and closely followed up with DU to ensure spontaneous resolution or no progression into the deep venous system. If a thrombus is extending into the deep system, treatment with anticoagulation is recommended with close follow-up using serial DU until thrombus resolution.

Treatment of chronic superficial venous insufficiency is associated with an improvement in the quality of life of patients. In a recent retrospective study of 135 patients (164 limbs) with a mean VCSS of 6 (range, 4–22), successful RFA treatment of the GSV was obtained in 98.2% of the cases. At a median follow-up of 11 months, the mean VCSS was 3.9 (range, 2–8), indicating a significant improvement from baseline.⁸⁹

Steam Ablation

Endovenous Steam Ablation (EVSA) is a recently developed technique by CermaVein to ablate saphenous veins using heated steam at 120°C. EVSA is done under tumescent anesthetic delivering steam pulsation across a saphenous vein using a small catheter and a steam generator. One advantage of CermaVein EVSA is the small size and flexibility of the catheters that can negotiate saphenous vein tortuosity. Experimental models suggest that 1 steam pulse/cm is likely to create heterogeneous results and is insufficient for vein ablation, whereas 2 to 3 pulses pulse/cm seem to be adequate.^{90,91} Also, experimental data suggest histopathologic changes after EVSA are similar to those after EVLA and EVRA, with high vein wall destruction and low perivenous wall damage.⁹² The experience with EVSA remains limited at this time. In a recent prospectively 1:1 between EVLT versus ClariVein in an observational study that included 46 patients treated with steam ablation compared with 37 treated with vein stripping, a faster return to daily and sporting activities was noted. There was also more sickness absence from work for those treated with vein stripping versus steam ablation (14 vs 2 days, respectively).⁹³

Nonthermal Ablative Therapies

Nonthermal ablative methods include sclerotherapy (liquid or foam, ultrasound guided, or non-ultrasound guided), catheter-assisted balloon sclerotherapy (CABS), ClariVein or mechanochemical endovenous ablation (MOCA), and cyanoacrylate adhesive (VenaSeal). The development of nonthermal ablation methods aims to reduce discomfort and heat-related complications that may result from EVHA such as pain, discomfort from applying the tumescent anesthetic, skin burns, and nerve injury (particularly of the sural nerve during SSV ablations).

Sclerotherapy

Sclerotherapy is a technique that uses a sclerosing agent injected with a fine needle directly into the vein. It is effective in ablating smaller spider and reticular veins but also used for ablating deeper (done under ultrasound guidance) saphenous veins, nonsaphenous tributaries, or incompletely treated saphenous veins. Sclerotherapy is also used for the treatment of persistent incompetent perforators after treatment of SSVs to enhance healing of venous ulceration.^{94,95} The sclerosing agent can be in liquid (generally used for the small spider or reticular veins) or foam (for the larger deeper veins). Sclerotherapy with ultrasound guidance for incompetent truncal and tributary varicose veins was shown to be highly effective.^{96,97} Foam sclerotherapy has several advantages to liquid therapy, including the need for smaller volume of sclerosing agent, lack of dilution with blood, better visibility with ultrasonography, and homogenous distribution in the injected vein.⁹⁸ The overall technical success with sclerotherapy is inferior to endothermal ablation, but patient-reported quality of life appears the same. Excellent patient satisfaction is achieved when truncal veins are treated with endothermal ablation followed by treatment of the tributaries with sclerotherapy.⁹⁹

Sclerotherapy causes intimal inflammation and thrombus formation, leading to fibrous tissue and obliteration of the injected vein. Sclerotherapy is contraindicated when the following are present:

- History of allergy to the sclerosant
- Pregnancy
- Lymphedema
- Thromboembolic risk (prior history of DVT, PE, active cancer, thrombophilia, or active superficial vein thrombosis)
- Known symptomatic intracardiac right-to-left shunt
- History of neurologic events after prior sclerotherapy treatments

Relative contraindications include history of multiple drug and nondrug allergies with anaphylaxis and history of migraine headaches with aura.

Complications of sclerotherapy are as follows:

- Neurosensory: migraine, transient blurred vision, transient ischemic attack and stroke (0.01%), and sensory and motor nerve damage (0.2%)
- Local: tissue necrosis, superficial thrombophlebitis (4.4%), venoarterial reflex vasospasm in adjacent arterioles, swelling and edema (0.5%), pigmentation (10%–30%), telangiectatic matting (15%–24%), and skin irritation
- Systemic: anaphylaxis, DVT (1%–3%), and pulmonary embolization^{100–104}

Several sclerosing agents¹⁰⁵ are available (Table 27.4), including detergents (sodium tetradecyl sulfate, polidocanol and sodium morrhuate), osmotic agents (hypertonic solution and sodium chloride solution with dextrose [Sclerodex]), and chemical irritants (chromated glycerin and polyiodinated iodine). The most commonly used ones are polidocanol, sodium tetradecyl sulfate, hypertonic solution, and chromated glycerin. Polidocanol causes less pigmentation, necrosis, and pain than sodium tetradecyl sulfate. Different concentrations are used for different vein

TABLE 27.4 Commonly Used Sclerosing Agents

GENERIC NAME	COMMERCIAL NAME	CONCENTRATION	INDICATIONS	SIDE EFFECTS
Polidocanol (laureth-9) (FDA approved)	Asclera	For spider veins: 0.5% For reticular veins: 1% Use 0.1–0.3 mL per injection and no more than 10 mL per session	Uncomplicated spider (≤ 1 mm) or reticular veins (1–3 mm) Not studied for veins ≥ 3 mm	Irritation, hematoma, discoloration, pain, pruritis, warmth, neovascularization, thrombosis
Polidocanol (FDA approved)	Varithena	Administered via a single cannula into the lumen of the target incompetent trunk veins or by direct injection into varicosities Use ≤ 5 mL per injection and no more than 15 mL per session After it is activated, injectable foam delivering a 1% solution	Incompetent GSVs, accessory saphenous veins, and visible varicosities of the GSV system above and below the knee	Irritation, hematoma, discoloration, hyperpigmentation, pain, pruritus, warmth, thrombosis, necrosis, neovascularization, anaphylaxis, dyspnea, vasculitis, palpitations, TIA or stroke, migraine, fainting, confusion, urticaria
Sodium tetradecyl sulfate (FDA approved)	Sotradecol	1% and 3% solutions Inject 0.5 mL followed by observation for several hours before additional injections Keep dose small using 0.5–2 mL (preferably 1 mL maximum) for each injection Maximum single treatment not to exceed 10 mL	Small uncomplicated varicose veins of the lower extremities (with competent valves) Do not use in acute superficial thrombophlebitis; valvular or deep vein incompetence; large superficial veins communicating to deeper veins; cellulitis; allergic conditions; infections; asthma; neoplasm; or Buerger disease	Irritation, hematoma, discoloration, pain, pruritis, warmth, neovascularization, thrombosis (including DVT and PE), tissue necrosis with extravasation, anaphylaxis, urticaria, asthmatic reaction
Morrhuate sodium (FDA approved)	Scleromate	Small or medium veins 50–100 mg (1–2 mL of 5% injection) Large veins, 150–250 mg (3–5 mL) May be repeated at 5-day to 7-day intervals	Uncomplicated varicose veins with competent valves Contraindicated if hypersensitivity to fatty acids; DVT; superficial thrombophlebitis; allergic conditions; infections; or asthma	Thrombosis (DVT, PE), valvular incompetency, vascular collapse, drowsiness, headache, dizziness, urticaria, nausea, burning at injection site, weakness, asthma
Hypertonic saline (not approved in United States as a sclerosing agent)	Hypertonic saline 23.4%	23.4% for reticular veins; 11.7% for spider veins	Treatment of reticular veins and spider veins Not for treatment of larger veins	Pain, burning, leg cramps, tissue necrosis, hemosiderin staining
72% chromated glycerin (no FDA approval in United States)	Sclermo	Maximum recommended dose is 10 mL per session (concentrations from 25%–100% have been used outside United States)	Spider and reticular veins	Pain upon injection (often compounded with lidocaine), highly allergenic, could lead to ureteral colic and hematuria

DVT, Deep vein thrombosis; FDA, Food and Drug Administration; GSV, great saphenous veins; PE, pulmonary embolism; TIA, transient ischemic attack.

sizes. Typically, the lowest appropriate concentration is used, and a low injection pressure is applied. Avoiding infiltration is important to reduce the chance of hyperpigmentation and skin necrosis. Hypertonic solution causes significant pain and marked staining. Chromated glycerin¹⁰⁶ is widely used in Europe. It also causes pain with injection, but its main advantage is the rare occurrence of hyperpigmentation, telangiectatic matting, and necrosis.

Catheter-Assisted Balloon Sclerotherapy

Catheter-assisted balloon sclerotherapy uses a targeted approach to deliver sclerotherapy to a particular segment of the GSV. Using a double-lumen catheter inserted in the GSV, a balloon is inflated at the tip of the catheter, which stops the blood flow. The second lumen is used to inject and aspirate the sclerosing agent. Early studies have shown a 90% closure rate of the GSV using this technique and with no serious side effects at 6-month follow-up.¹⁰⁷ More data are needed to determine how this technique

compares with the more established techniques of EVLA and EVRA.

ClariVein or Mechanochemical Endovenous Ablation

Mechanochemical endovenous ablation uses the ClariVein catheter (Vascular Insights), which allows mechanical injury to the vessel coupled with the administration of a sclerosing agent. Using this technique, tumescent anesthetic is not required. The ClariVein catheter is positioned within the saphenous vein under ultrasound guidance, and the distal tip is positioned 2 cm distal to the SFJ. A metal wire with a small ball at the tip runs through the catheter and induces vein wall injury by rotating at 3500 rpm for 2 to 3 seconds. The sclerosing agent is infused simultaneously with the wire rotation. Data suggest that this technique is effective in obliterating the GSV. In one study, 87% of GSV were closed at 6-weeks follow-up and with an improvement in VCSS.¹⁰⁸



In another study of 29 patients, primary closure was achieved in 96.7% of patients at 6 months of follow-up. MOCA was also applied in SSV successfully.¹⁰⁹ In a study of 50 patients, the 1-year ablation success rate was 94% and with no major complications. Also the VCSS was reduced significantly.¹¹⁰ Complications of this procedure included localized ecchymosis, induration at access site, and superficial thrombophlebitis with no nerve injury, DVT, or necrosis.¹¹⁰

Finally, 152 patients were randomized 1:1 between EVLT versus ClariVein in treating patients with superficial vein incompetence (A Randomized Controlled Trial of Endovenous Laser Ablation Versus Mechanochemical Ablation With ClariVein in the Management of Superficial Venous Incompetence [LAMA] Trial). Both groups had low intraprocedural pain scores ($P = .210$). At 1-year follow-up, EVLT had a 91% occlusion rate versus 77% in the MOCA group ($P = .020$), but both groups had similar improvement in VCSS and the Aberdeen Varicose Vein Questionnaire (AVVQ).¹¹¹

Cyanoacrylate Adhesive

Cyanoacrylate adhesive or VenaSeal (Medtronic) is a tissue adhesive that polymerizes on contact with anionic substances such as blood or plasma and induces an inflammatory damage to the vein wall.¹¹² The adhesive eventually undergoes resorption and is replaced with fibrous tissue. The delivery of cyanoacrylate does not require tumescent anesthetic. Early data suggest complete occlusion of the GSV in 92% of patients with significant improvement in VCSS scores.¹¹³ In a multi-institutional retrospective review of 119 patients (68 treated with RFA and 51 with VenaSeal) with CEAP class 6 and followed for a median of 105 days, the median time to wound healing after the procedure was significantly shorter for VenaSeal than for RFA (43 vs 104 days; $P = .001$). The ulcer recurrence rate was similar at 22.1% for RFA versus 13.7% for VenaSeal ($P = .25$).¹¹⁴ In a 60-month extension study from the randomized VeClose study of 89 symptomatic venous insufficiency patients (CEAP class C2–C4b) and GSV reflux (47 cyanoacrylate group, 33 from the RFA group, and 9 cyanoacrylate roll-in patients), Kaplan-Meier estimates for freedom from recanalization in the randomized cyanoacrylate and RFA groups were 91.4% and 85.2%, respectively (no significant difference). Quality of life was also similar at 60 months.¹¹⁵

Hypersensitivity reaction presenting as an erythematous rash was reported with cyanoacrylate adhesive closure. In a combined retrospective/prospective review, 379 limbs were treated in 286 patients. Hypersensitivity reactions occurred in 5.8% treatments or 6.3% of patients. A total of 4.2% were mild, 1.3% moderate, and 0.3% severe. Reactions occurred between 1 and 23 days, with a mean of 13 days, and lasted from 3 to 28 days (mean 10.8 ± 4.9 days).¹¹⁶

Hypersensitivity reactions occurred in 6.0% of patients treated with cyanoacrylate adhesive closure, but most were mild and self-limited. Severe reactions were uncommon. No predictive patient or procedural factors were found to be associated with hypersensitivity reactions other than a trend toward decreased risk in patients with advanced CEAP clinical class. Previous cyanoacrylate adhesive closure treatment was not a predictive factor for hypersensitivity reaction in patients undergoing treatment at a later date.

Phlebectomy

Phlebectomy is the removal of varicose veins using microsurgical techniques by creating sequential 2-mm skin incisions along the course of the vein followed by its extraction with a hook. Robert Muller, a dermatologist from Switzerland in the mid-1950s, refined this technique. It is carried out under local anesthetic on an outpatient basis. This technique needs to be avoided in patients with skin infections near the phlebectomy site or severe lower extremity edema and in patients on anticoagulation or who have thrombophilia.¹¹⁷ In this technique, the veins are marked preoperatively in the standing position. Phlebectomy should be performed first below the knee when done in the setting of EVHA or ligation and stripping of either the GSV or SSV. It is recommended, however, that phlebectomy be performed several weeks after treating the GSV or SSV.¹¹⁷ Complications of phlebectomy include infection, induration, hyperpigmentation and tattooing, hypopigmentation (incision site), keloid tissue, swelling, ischemia, tissue necrosis, bleeding, superficial thrombophlebitis, DVT, edema, nerve damage, and neuroma.^{117,118}

Surgical Vein Stripping

Surgical stripping and ligation (S&L) has been widely replaced with endovascular vein obliteration. It is generally performed under local or general anesthesia and is an outpatient procedure. One or more incisions are made over the large varicosities; the vein is tied off and removed using a stripper. A recent randomized trial showed that EVLA and S&L were similar in clinical and ultrasonography recurrences of varicose veins at 2 years of follow-up. In this study, 121 patients were randomized to EVLA versus S&L of the GSV from the SFJ. Recurrence of varicose veins occurred in 26% and 37% of EVLA and surgery, respectively (not significant). The sources of reflux were also the same in both groups.¹¹⁹ In addition, in another randomized trial of EVLA, ultrasound-guided sclerotherapy, and S&L, EVLA was superior to ultrasound-guided sclerotherapy and equally effective to S&L in obliterating the GSV at 1 year.¹²⁰ In addition, in a recent randomized trial, EVRA was compared with S&L and showed that EVRA had early advantages over S&L with quicker recovery, less pain scores, and an earlier return to work. The magnitude of the differences became less between 1 week and 4 months follow-up.¹²¹ Predictors of recurrent varicose veins after S&L appear to be the presence of neovascularization, incompetent superficial vessel in the thigh, or incompetent SFJ at 2 years follow-up postoperatively. Recurrence of varicosities was associated with a worse Aberdeen Varicose Vein Symptom Severity Score.¹²²

Pharmacologic Management of Chronic Venous Insufficiency

There are several mechanisms postulated as the cause of symptoms and structural changes in patients with CVI. Venous wall tension and hypoxia of the venous wall are likely to be underlying mechanisms for generating pain in

the early phases of venous insufficiency. Hemorheological disorders with increased blood viscosity are likely to worsen the hypoxic injury to the vessel wall, which triggers an inflammatory reaction leading also to pain and restlessness. Venous pressures along with increase in capillary permeability caused by inflammation lead to edema. Eventually, the inflammatory reaction triggered by oxygen free radicals and leukocyte-endothelial interaction lead to the release of multiple inflammatory mediators, growth factors, and proteolytic enzymes that may be directly responsible for the structural and permanent damage seen in patients with CVI. Although the mainstay of treatment is to reduce venous pressures and obliterate refluxing veins, pharmacologic management may have a role in the management of these patients.¹²³

There is no current standard in the use of phlebotropic drugs in the management of CVI. These drugs are currently not approved in the United States for treating CVI but have been in use as alternative therapy in Europe for treating CVI:

1. Benzopyrones
 - a. α -Benzopyrones: 5,6-Benzo-[α]-pyrone (also known as coumarin) increases proteolysis by activating tissue macrophages.¹²⁴ Protein removal allows a steady reduction in edema and inflammation.¹²⁵ Coumarin is not an anticoagulant like 4-hydroxycoumarins, which also belong to the same class.
 - b. Chromenones (flavonoids or γ -benzopyrones): These include micronized purified flavonoid fraction (MPFF) (Daflon), diosmin, diosmethin, rutin, oxerutins, and others. MPFF contains 90% diosmin. It reduces inflammation by inhibiting endothelial activation. In randomized trials, MPFF shortened the time for ulcer healing and reduced edema and symptoms of reflux. In addition, it may delay the reflux and the appearance of varicosities.¹²⁶ In addition, oxerutins were shown to be significantly better than placebo in controlling symptoms and objective findings of chronic venous hypertension.¹²⁷
2. Saponosides: Randomized trials have shown that horse-chestnut extract (*Aesculus hippocastanum*) is effective in reducing symptoms of edema comparable to compression stockings and significantly better than placebo.^{123,128-130} The long-term effectiveness and safety are not yet clear, but short-term use seems to be safe and reasonably well tolerated with improvement in patients' symptoms.
3. Synthetic products: These include calcium dobesilate, benzarone, and naftazone. Dobesilate reduces capillary permeability and platelet aggregation with an increase in endothelium-dependent relaxation secondary to nitric oxide synthesis.¹³¹ A meta-analysis of randomized trials suggested that dobesilate is more effective than placebo in improving night cramps, paresthesias, and swelling with higher efficacy in patients with more severe disease.¹³² A recent double-blind multicenter trial showed that dobesilate improves quality of life at 12-month follow-up but was not significantly different from placebo at 3 months.¹³³ Naftazone has been shown by the French Venous Naftazone trial group¹³⁴ to reduce disability and leg swelling from uncomplicated symptomatic varicose veins in women.

ENDOVASCULAR MANAGEMENT OF VENOUS ULCERATIONS

Venous ulcerations account for 60% to 80% of ulcers seen in the lower extremity.¹³⁵ The incidence is higher in women than men (20.4 vs 14.6 per 100,000 person-years) and increases with age. The incidence of venous ulceration has not changed substantially since 1981.¹³⁶ An early conservative approach with high compression bandages or stockings has been the traditional approach. However, recent data suggest that compression therapy with early rather than deferred endovenous treatment results in faster ulcer healing.¹³⁷ In a two-arm, multicenter, parallel-group, open randomized controlled trial in patients with venous ulcers, 450 patients were randomized 1:1 to either early ablation (compression therapy and superficial endovenous ablation within 2 weeks of randomization) or deferred ablation (compression therapy). Time to ulcer healing was shorter in the early superficial endovenous ablation (hazard ratio, 1.38; 95% CI, 1.13–1.68; $P = .001$). Median time to ulcer healing was also shorter at 56 (95% CI, 49–66) days in the early ablation group versus 82 (95% CI, 69–92) days in the deferred ablation group. More patients experienced (85.6% vs 76.3%) ulcer healing in the early ablation group. Prior studies also showed that the 24-week healing rate with compression alone was 65%.¹³⁸ The duration of the ulcer and the size are high predictors to complete healing and to the time to heal. Smaller and more recent ulcers tend to heal more frequently and in a shorter duration of time: 72% of ulcers smaller than 5 cm² healed at a mean time of 7.5 weeks, and 40% of ulcers larger than 5 cm² healed at 9.8 weeks; 64% of ulcers of less than 1-year duration healed, and 24% of those with more than a 3-year duration healed.¹³⁹

The combination of compression stockings with surgical treatment of refluxing veins resulted in a reduction in 12-month recurrence of venous ulcerations compared with compression therapy alone (12% vs 28%; $P < .0001$).¹³⁸ At 24 weeks, the healing rate, however, was statistically similar between the two strategies (65% vs 65%).¹³⁸ In another randomized trial, however, the healing rate was faster after surgical treatment followed by 20- to 30-mm Hg elastic compression stockings compared with foam dressing, zinc oxide, and an inelastic bandage. Healing occurred at 31 days with surgery and 63 days with compression alone. In addition, at 3-year follow-up, the recurrence rate was reduced with surgery to 9% versus 38% in the compression group ($P < .05$) with a better improvement in the quality of life in the surgical group.¹³⁹ Several surgical approaches to treat refluxing veins and perforators have been developed, including ligation and stripping for the saphenous veins and endoscopic and open subfascial division of incompetent perforating veins.^{121,140} Currently, endovascular techniques are increasingly used more often and are largely replacing the surgical options.

Refluxing perforators are highly prevalent in venous ulcers and have been linked to the formation of chronic ulcerations¹⁴¹ (Figure 27.17). Perforators are an important therapeutic target in patients with venous ulcers. Currently, perforators larger or equal to 3.5 mm and with a minimum of 0.5 seconds reflux located at the ulcer¹⁴² or

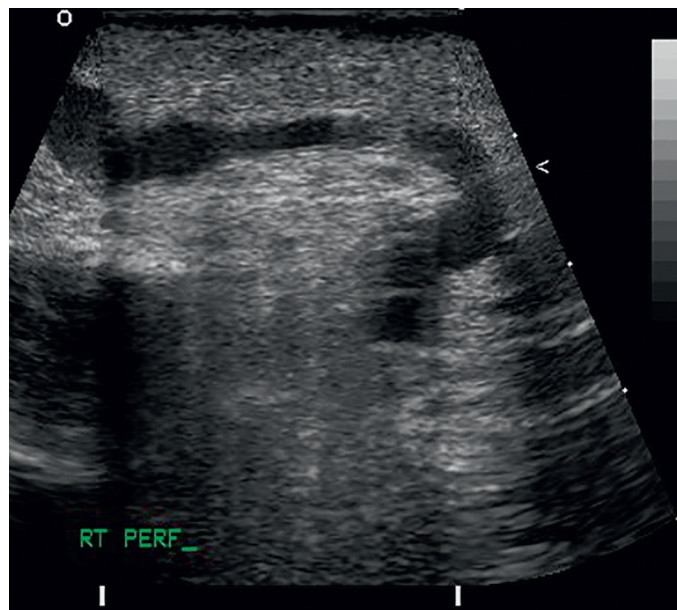


FIGURE 27.17 Right posterior tibial perforator.

refluxing via tributaries to the ulcer are a target for treatment when conservative management or ablation of the SSVs has failed in healing the ulceration. Treatment of the refluxing truncal saphenous veins may lead to healing of ulcerations without treatment of perforators.^{143,144} It is prudent to treat refluxing saphenous veins first along with compression therapy and wound management before ablation of perforators. A recent analysis of published data indicated that additional ablative procedures of incompetent perforating veins and persistent superficial reflux in combination to compression therapy is effective in healing persistent or recurrent venous ulcers after treatment of superficial venous reflux.¹⁴⁵ For medial ulcers, the focus needs to be on the posterior tibial perforators and for lateral malleolar ulcerations on the lateral calf and ankle perforators.¹⁴⁶ Endovascular techniques have emerged as an effective treatment of refluxing perforators. These include RFA,^{146,147} laser ablation,¹⁴⁸ and ultrasound-guided foam sclerotherapy.¹⁴⁹

The endovascular management of patients with venous ulcerations should focus on evaluating the deep system. It is important to rule out DVT and proximal venous obstruction. Abnormal spectral Doppler flow in one CFV compared with the other should raise suspicion of proximal venous obstruction. In select patients, CTV or MRV is needed to rule out proximal venous compression. Predictors of failure after treatment of refluxing perforators should raise suspicion for abnormal proximal venous flow.¹⁵⁰ In addition, identifying proximal venous obstruction and treating it in patients with deep venous reflux may be sufficient to alleviate the symptoms and achieve the desired outcome from the treatment with no adverse effect on the deep reflux.¹⁵¹ In a retrospective analysis of 157 patients, ulcer healing rates at 1 year were 86.8% and 65.6% in the superficial vein treatment and iliac stenting group versus the superficial vein treatment only group, respectively ($P = .001$). The iliac vein stent group also had

an improved venous clinical severity score compared with the nonstent group (8.3 vs 11.7, respectively; $P = .01$). This study supports that a combined treatment of the deep venous system and the superficial venous system in patients with venous ulcerations is associated with a better ulcer healing.¹⁵²

DEEP VENOUS VALVES

Deep venous valve dysfunction has been the subject of considerable research. Currently, there is no consensus on treating the deep venous valves. Deep venous valve reflux can contribute to the development of progressive CVI, leading to ulcerations and disability. Treatment of the deep venous valves is a target in patients with advanced symptoms of ulceration and impaired quality of life.

An open surgical technique to treat the FV valves has been described in a select group of patients with postphlebotic syndrome.¹⁵³ In this procedure, the valve underwent primary repair with a “series of tucking sutures and shortening the cusp.”¹⁵⁴ Ulcer healing was accomplished in 90% of patients. A modification on this open technique is external venous valve repair (transcommisural valvuloplasty), which was described in a series of 179 patients with significant improvement of pain and swelling, and cumulative ulcer recurrence-free interval of 63% at 30 months.¹⁵⁴ This technique involved “placing transluminal sutures along the valve attachment lines, which simultaneously closed the valve attachment angle and also tightened the valve cusps.” Complications included bleeding, venothromboembolic disease, and infections. Another surgical approach in patients with damaged, nonrepairable valves (post-DVT) was valve transposition from the profunda femoris, axillary, or saphenous veins using vein substitution techniques¹⁵⁵ or the use of cryopreserved valve to the femoropopliteal vein.¹⁵⁶ A high failure rate was seen with the cryovalves, including acute rejection and early and late occlusion. Patent and competent cryovalves at 24 months were 41% and 27%, respectively. There was no change in pain relief or degree of swelling. The ulcer recurrence-free rate at 36 months was 50%. Finally, the construction of neo-valve¹⁵⁷ in the deep venous system seems to improve reflux and healing at a median follow-up period of 5 months.¹⁵⁸ These data need to be duplicated in a larger sample and be sustained on longer follow-up. Successful treatment of deep venous refluxing valves with no repair options (as seen in end-stage venous insufficiency or postthrombotic cases) has so far been in autogenous valve transfer using surgical techniques.¹⁵⁹ There have not been any successful options for transplanting allograft or xenograft valves despite pretreatment of the valve with various methods to reduce its immunogenicity before implantation.

Transcatheter deep valve repair is a nonsurgical approach that is currently under intense investigation and remains well in its very early stages. In a goat animal model,¹⁶⁰ endoscopic harvesting of a valve-containing segment of external jugular vein, sutured within a self-expanding Wallstent, was compressed and delivered through a 12-Fr sheath to the contralateral external jugular

vein. At 6 weeks, the valve remained intact, and five of the six valves were competent. To date, this observation has not been translated into a clinical application. In an ovine model,¹⁶¹ percutaneous autogenous venous valves from harvested jugular veins were mounted on a stent template and delivered into the contralateral jugular vein using a percutaneous femoral approach. At 3-month follow-up, eight of nine valves were intact and nonthickened and were free of thrombus. Recently, in a sheep model,¹⁶² a segment of vein from the internal jugular with a venous valve was mounted on a circumferential barbed stent and deployed into the contralateral internal jugular vein. At 6 months, there was no thrombus, tilting, migration, or incompetence in these valves. On the other hand, using a valve-containing vein segment harvested from a bovine jugular vein preserved in glutaraldehyde and mounted on a balloon-expandable stent in six lambs in the inferior vena cava yielded total occlusions of these valves in 2 months.¹⁶³ It is unclear whether this was the result of barotrauma of the balloon-expandable stent, the xenograft material, or the bulk of metal on the stent.¹⁵⁹ The percutaneous outcomes were similar to those of surgery. The autograft seems to have the most reliable success when implanted percutaneously or surgically.

Several valve designs are currently in research with a particular focus on tissue-engineered valves. Prosthetic valves fabricated by electrospinning and consisting of polyurethane fiber scaffolds,¹⁶⁴ autologous cell-derived tissue engineered venous valves on fully biodegradable scaffolds,¹⁶⁵ and porcine small intestinal submucosa bioprosthetic valves with endothelial progenitor outgrowth cells as a source of endothelialization.¹⁶⁶ Venous PercValve with eNitinol membranes are also currently in development. NiTi, or nitinol, is a nickel-titanium alloy that is biologically inert, has shape memory, and could be made in ultrathin membranes (eNitinol) that are flexible enough to be used in valve development.¹⁶⁷ Finally, improvements are ongoing on the stent delivery system with no barbs on the stents to minimize vessel wall injury¹⁶⁸ and with minimal metal struts exposed to the circulation.

Recently, the Internal Compression Therapy (ICT) Paravalvular Leak Device (Invamed) was introduced as a potential therapy for refluxing deep valves. It consists of an injection pump that delivers a combination of hyaluronic acid and n-butyl-cyanoacrylate (n-BCA) hard gel between the deep vein and muscle fascia to close the gap between the vein valves. In a recent study of 286 patients with deep venous insufficiency, the technical success rate was 100%. At the 1-year follow-up, the overall success rate was 92% with no significant morbidity or mortality. VCSS scores improved from 20.7 ± 5.9 at baseline to 3.9 ± 0.9 after treatment ($P < .001$).¹⁶⁹

CONCLUSIONS

There has been less emphasis on the venous system in general medical education. More than 25 million people in the United States have progressive CVD, which eventually leads to venous hypertension, venous insufficiency, hyperpigmentation, and disabling venous ulcerations. The

venous anatomy and physiology are complex, and understanding them is important to correctly identify and treat patients with superficial venous disease. Different safe and effective percutaneous methods have evolved in treating the superficial venous system, and surgical vein stripping is now infrequently performed. A complex relationship exists between the superficial and deep venous system. A full evaluation of the patient is important, and a detailed mapping to the venous circulatory network is required for an effective therapeutic strategy. Percutaneous valve transplantation to the deep venous system may become an important future therapy in symptomatic patients with deep venous reflux.

Visit Elsevier eBooks+ to access the complete list of references.

SELECTED REFERENCES

- Robertson L, Evans C, Fowkes FG. Epidemiology of chronic venous disease. *Phlebology*. 2008;23:103-111.
- Coon WW, Willis PW III, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh community health study. *Circulation*. 1973;48:839-846.
- Criqui MH, Jamosmos M, Fronek A, et al. Chronic venous disease in an ethnically diverse population: the San Diego Population Study. *Am J Epidemiol*. 2003;158:448-456.
- Lee AJ, Evans CJ, Allan PL, et al. Lifestyle factors and the risk of varicose veins: Edinburgh Vein Study. *J Clin Epidemiol*. 2003;56:171-179.
- McGuckin M, Waterman R, Brooks J, et al. Validation of venous leg ulcer guidelines in the United States and United Kingdom. *Am J Surg*. 2002;183:132-137.
- Cavezzi A, Labropoulos N, Partsch H, et al. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs—UIP consensus document. Part II. Anatomy. *Eur J Vasc Endovasc Surg*. 2006;31:288-299.
- Caggiati A, Bergan JJ, Gloviczki P, et al. International interdisciplinary consensus committee on venous anatomical terminology. Nomenclature of the veins of the lower limbs: an international interdisciplinary consensus statement. *J Vasc Surg*. 2002;36:416-422.
- Schul MW, Vayuvegula S, Keaton TJ. The clinical relevance of anterior accessory great saphenous vein reflux. *J Vasc Surg Venous Lymphat Disord*. 2020;8(6):1014-1020.
- Mozes G, Carmichael SW, Gloviczki P. Development and anatomy of the venous system. In: Gloviczki P, Yao JS, eds. *Handbook of Venous Disorders*. 2nd ed. Arnold Publisher; 2001:11-24.
- Eberhardt RT, Raffetto JD. Chronic venous insufficiency. *Circulation*. 2005;111:2398-2409.
- Franzeck UK, Haselbach P, Speiser D, Bollinger A. Microangiopathy of cutaneous blood and lymphatic capillaries in chronic venous insufficiency (CVI). *Yale J Biol Med*. 1993;66:37-46.
- Browne NL, Burnand KG. The cause of venous ulceration. *Lancet*. 1982;2:243-245.
- Eklöf B, Rutherford RB, Bergan JJ, et al. American Venous Forum International Ad Hoc Committee for Revision of the CEAP Classification. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg*. 2004;40:1248-1252.
- Vasquez MA, Rabe E, McLafferty RB, et al. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. *J Vasc Surg*. 2010;52:1387-1396.
- Rutherford RB, Padberg FT Jr, Comerota AJ, et al. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg*. 2000;31:1307-1312.
- Fowler B, Zygmunt J, Ramirez H, Kolluri R. Venous insufficiency evaluation with duplex scanning. *J Vasc Ultrasound*. 2014;38(1):34-40.
- Belcaro G, Labropoulos N, Christopoulos D, et al. Noninvasive tests in venous insufficiency. *J Cardiovasc Surg (Torino)*. 1993;34:3-11.
- Ibegbuna V, Delis KT, Nicolaides AN. Haemodynamic and clinical impact of superficial, deep and perforator vein incompetence. *Eur J Vasc Endovasc Surg*. 2006;31:535-541.
- Ulukan MO, Karakaya A, Erkanli K, et al. Efficiency of prophylactic ablation of the tributary venous pathways draining around the saphenofemoral junction to decrease the rate of future varicose vein and symptoms occurrence. *Ann Vasc Surg*. 2021;75:267-274.
- Labropoulos N, Giannoukas AD, Delis K, et al. Where does venous reflux start? *J Vasc Surg*. 1997;26:736-742.
- Sales CM, Bilof ML, Petrillo KA, Luka NL. Correction of lower extremity deep venous incompetence by ablation of superficial venous reflux. *Ann Vasc Surg*. 1996;10:186-189.
- Nishibe T, Nishibe M, Akiyama S. Influence of superficial venous ablation on deep venous dilation and reflux in patients with saphenous varicose veins. *Vasc Endovascular Surg*. 2020;54(8):687-691.



62. Mussa FF, Peden EK, Zhou W, et al. Iliac vein stenting for chronic venous insufficiency. *Tex Heart Inst J*. 2007;34:60-66.
64. Felty CL, Rooke TW. Compression therapy for chronic venous insufficiency. *Semin Vasc Surg*. 2005;18:36-40.
67. Mosti G, Cavezzi A, Bastiani L, Partsch H. Compression therapy is not contraindicated in diabetic patients with venous or mixed leg ulcer. *J Clin Med*. 2020;9(11):3709.
71. Vuylsteke ME, Mordon SR. Endovenous laser ablation: a review of mechanisms of action. *Ann Vasc Surg*. 2012;26:424-433.
74. Almeida J, Mackay E, Javier J, et al. Saphenous laser ablation at 1470 nm targets the vein wall, not blood. *Vasc Endovascular Surg*. 2009;43:467-472.
77. Timperman PE, Sichlau M, Ryu RK. Greater energy delivery improves treatment success of endovenous laser treatment of incompetent saphenous veins. *J Vasc Interv Radiol*. 2004;15:1061-1063.
81. Christenson JT, Gueddi S, Gemayel G, Bounameaux H. Prospective randomized trial comparing endovenous laser ablation and surgery for treatment of primary great saphenous varicose veins with a 2-year follow-up. *J Vasc Surg*. 2010;52:1234-1241.
83. Lurie F, Creton D, Eklof B, et al. Reprinted article "Prospective randomised study of endovenous radiofrequency obliteration (closure) versus ligation and vein stripping (EVOLVeS): two-year follow up." *Eur J Vasc Endovasc Surg*. 2011;42(suppl 1):S107-S113.
84. Rasmussen LH, Lawaetz M, Bjoern L, et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. *Br J Surg*. 2011;98:1079-1087.
85. Marsh P, Price BA, Holdstock J, et al. Deep Vein Thrombosis (DVT) after venous thermoablation techniques: rates of Endovenous Heat-induced Thrombosis (EHIT) and classical DVT after radiofrequency and endovenous laser ablation in a single centre. *Eur J Vasc Endovasc Surg*. 2010;40:521-527.
86. Sadek M, Kabnick LS, Rockman CB, et al. Increasing ablation distance peripheral to the saphenofemoral junction may result in a diminished rate of endothermal heat-induced thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2013;1:257-262.
88. Healy DA, Kimura S, Power D, et al. A systematic review and meta-analysis of thrombotic events following endovenous thermal ablation of the great saphenous vein. *Eur J Vasc Endovasc Surg*. 2018;56(3):410-424.
89. Borghese O, Pisani A, Di Centa I. Endovenous radiofrequency for chronic superficial venous insufficiency: clinical outcomes and impact in quality of life. *J Med Vasc*. 2021;46(1):3-8.
90. van den Bos RR, Milleret R, Neumann M, Nijsten T. Proof-of-principle study of steam ablation as novel thermal therapy for saphenous varicose veins. *J Vasc Surg*. 2011;53:181-186.
91. van Ruijven PW, van den Bos RR, Alazard LM, et al. Temperature measurements for dose-finding in steam ablation. *J Vasc Surg*. 2011;53:1454-1456.
92. Thomis S, Verbrugghe P, Milleret R, et al. Steam ablation versus radiofrequency and laser ablation: an in vivo histological comparative trial. *Eur J Vasc Endovasc Surg*. 2013;46:378-382.
93. Lislegaard Næs A-K, Halsteinli V, Seternes A. Steam ablation versus stripping of great saphenous varicose veins. *Tidsskr Nor Laegeforen*. 2019;139(5).
94. Pang KH, Bate GR, Darvall KA, et al. Healing and recurrence rates following ultrasound-guided foam sclerotherapy of superficial venous reflux in patients with chronic venous ulceration. *Eur J Vasc Endovasc Surg*. 2010;40:790-795.
95. Memetoglu ME, Yilmaz M, Kehlibar T. Ultrasonography-guided foam sclerotherapy in patients with small saphenous vein insufficiency. *J Vasc Surg Venous Lymphat Disord*. 2020;8(5):799-804.
96. Rathbun S, Norris A, Morrison N, et al. Performance of endovenous foam sclerotherapy in the USA for the treatment of venous disorders: ACP/SVM/AVF/SIR quality improvement guidelines. *Phlebology*. 2014;29:76-82.
99. Cartee TV, Wirth P, Greene A, et al. Ultrasound-guided foam sclerotherapy is safe and effective in the management of superficial venous insufficiency of the lower extremity. *J Vasc Surg Venous Lymphat Disord*. 2021;9(4):1031-1040.
100. Cavezzi A, Parsi K. Complications of foam sclerotherapy. *Phlebology*. 2012;27(suppl 1):46-51.
103. Guex J-J, Allaert F-A, Gillet J-L, et al. Immediate and midterm complications of sclerotherapy: report of a prospective multicenter registry of 12,173 sclerotherapy sessions. *Dermatol Surg*. 2005;31:123-128.
108. Van Eekeren RRJP, Boersma D, Elias S, et al. Endovenous mechanochemical ablation of great saphenous vein incompetence using the ClariVein device: a safety study. *J Endovasc Ther*. 2011;18:328-334.
111. Mohamed AH, Leung C, Wallace T. A randomized controlled trial of endovenous laser ablation versus mechanochemical ablation with ClariVein in the Management of Superficial Venous Incompetence (LAMA trial). *Ann Surg*. 2021;273(6):e188-e195.
114. O'Banion LA, Reynolds KB, Kochubey M, et al. Treatment of superficial venous reflux in CEAP 6 patients: a comparison of cyanoacrylate glue and radiofrequency ablation techniques. *J Vasc Surg Venous Lymphat Disord*. 2021;9(5):1215-1221.
115. Morrison N, Gibson K, Vasquez M. Five-year extension study of patients from a randomized clinical trial (VeClose) comparing cyanoacrylate closure versus radiofrequency ablation for the treatment of incompetent great saphenous veins. *J Vasc Surg Venous Lymphat Disord*. 2020;8(6):978-989.
119. Rasmussen LH, Bjoern L, Lawaetz M, et al. Randomised clinical trial comparing endovenous laser ablation with stripping of the great saphenous vein: clinical outcome and recurrence after 2 years. *Eur J Vasc Endovasc Surg*. 2010;39:630-635.
121. Lurie F, Creton D, Eklof B, et al. Prospective randomized study of endovenous radiofrequency obliteration (closure procedure) versus ligation and stripping in a selected patient population (EVOLVeS Study). *J Vasc Surg*. 2003;38:207-214.
137. Gohel MS, Heatley F, Liu X. Early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration: the EVRA RCT. *Health Technol Assess*. 2019;23(24):1-96.
138. Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. *Lancet*. 2004;363:1854-1859.
146. Lawrence PF, Alktaifi A, Rigberg D, et al. Endovenous ablation of incompetent perforating veins is effective treatment for recalcitrant venous ulcers. *J Vasc Surg*. 2011;54:737-742.
152. Yang X, Wu X, Peng Z, et al. Outcomes of endovenous laser ablation with additional iliac vein stenting of nonthrombotic lesions in patients presenting with active venous ulcers. *J Vasc Surg Venous Lymphat Disord*. 2021;9(6):1517-1525.

REFERENCES

- White JV, Ryjowski C. Chronic venous insufficiency. *Perspect Vasc Surg Endovasc Ther*. 2005;17:319-327.
- Evans CJ, Fowkes FG, Ruckley CV, et al. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. *J Epidemiol Community Health*. 1999;53:149-153.
- Robertson L, Evans C, Fowkes FG. Epidemiology of chronic venous disease. *Phlebology*. 2008;23:103-111.
- Ruckley CV, Evans CJ, Allan PL, et al. Chronic venous insufficiency: clinical and duplex correlations. The Edinburgh Vein Study of venous disorders in the general population. *J Vasc Surg*. 2002;36:520-525.
- Coon WW, Willis PW III, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh community health study. *Circulation*. 1973;48:839-846.
- Kurz X, Kahn SR, Abenham L, et al. Chronic venous disorders of the leg: epidemiology, outcomes, diagnosis and management. Summary of an evidence-based report of the VEINES task force. Venous Insufficiency Epidemiologic and Economic Studies. *Int Angiol*. 1999;18:83-102.
- Moffatt CJ, Franks PJ, Doherty DC, et al. Prevalence of leg ulceration in a London population. *QJM*. 2004;97:431-437.
- Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: the Framingham Study. *Am J Prev Med*. 1988;4:96-101.
- Robertson L, Lee AJ, Evans CJ, et al. Incidence of chronic venous disease in the Edinburgh Vein Study. *J Vasc Surg Venous Lymphat Disord*. 2013;1:59-67.
- Cesarone MR, Belcaro G, Nicolaides AN, et al. 'Real' epidemiology of varicose veins and chronic venous diseases: the San Valentino Vascular Screening Project. *Angiology*. 2002;53:119-130.
- Criqui MH, Jamosmos M, Fronek A, et al. Chronic venous disease in an ethnically diverse population: the San Diego Population Study. *Am J Epidemiol*. 2003;158:448-456.
- Mekky S, Schilling RSF, Walford J. Varicose veins in women cotton workers. An epidemiological study in England and Egypt. *BMJ*. 1969;2:591-595.
- Lee AJ, Evans CJ, Allan PL, et al. Lifestyle factors and the risk of varicose veins: Edinburgh Vein Study. *J Clin Epidemiol*. 2003;56:171-179.
- Laurikka JO, Sisto T, Tarkka MR, et al. Risk indicators for varicose veins in forty- to sixty-year-olds in the Tampere Varicose Vein Study. *World J Surg*. 2002;26:648-651.
- Chiesa R, Marone EM, Limoni C, et al. Demographic factors and their relationship with the presence of CVI signs in Italy: the 24-cities cohort study. *Eur J Vasc Endovasc Surg*. 2005;30:674-680.
- Ahmed T, Portnoy R, Chachati G, et al. Correlation of body mass index with recanalization risk after endovenous thermal ablation. *J Vasc Surg Venous Lymphat Disord*. 2022;10(1):82-86.
- McGuckin M, Waterman R, Brooks J, et al. Validation of venous leg ulcer guidelines in the United States and United Kingdom. *Am J Surg*. 2002;183:132-137.
- Lafuma A, Fagnani F, Peltier-Pujol F, Rauss A. Venous disease in France: an unrecognized public health problem [in French]. *J Mal Vasc*. 1994;19:185-189.
- Dinkel R. Venous disorders, a cost intensive disease. *Phlebology*. 1997;26:164-168.
- Tennvall GR, Andersson K, Bjellerup M, et al. Treatment of venous leg ulcers can be better and cheaper. Annual costs calculation based on an inquiry study. *Lakartidningen*. 2004;101:1506-1510, 1512-1513.
- Callam MJ, Harper DR, Dale JJ, Ruckley CV. Chronic ulcer of the leg: clinical history. *BMJ*. 1987;294:1389-1391.
- Da Silva A, Navarro MF, Batalheiro J. The importance of chronic venous insufficiency: various preliminary data on its medico-social consequences [in French]. *Phlebologie*. 1992;45:439-443.
- Cavezzi A, Labropoulos N, Partsch H, et al. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs—UIP consensus document. Part II. Anatomy. *Eur J Vasc Endovasc Surg*. 2006;31:288-299.
- Caggiati A, Bergan JJ, Gloviczki P, et al. International interdisciplinary consensus committee on venous anatomical terminology. Nomenclature of the veins of the lower limbs: an international interdisciplinary consensus statement. *J Vasc Surg*. 2002;36:416-422.
- Schul MW, Vayuvegula S, Keaton TJ. The clinical relevance of anterior accessory great saphenous vein reflux. *J Vasc Surg Venous Lymphat Disord*. 2020;8(6):1014-1020.
- Mozes G, Carmichael SW, Gloviczki P. Development and anatomy of the venous system. In: Gloviczki P, Yao JS, eds. *Handbook of Venous Disorders*. 2nd ed. Arnold Publisher; 2001:11-24.
- Eberhardt RT, Raffetto JD. Chronic venous insufficiency. *Circulation*. 2005;111:2398-2409.
- Burnand KG. The physiology and hemodynamics of chronic venous insufficiency of the lower limbs. In: Gloviczki P, Yao JS, eds. *Handbook of Venous Disorders*. 2nd ed. Arnold Publisher; 2001:49-57.
- Neglén P, Thrasher TL, Raju S. Venous outflow obstruction: an underestimated contributor to chronic venous disease. *J Vasc Surg*. 2003;38:879-885.
- Araki CT, Back TL, Padberg FT, et al. The significance of calf muscle pump function in venous ulceration. *J Vasc Surg*. 1994;20:872-877.
- Christopoulos D, Nicolaides AN, Cook A, et al. Pathogenesis of venous ulceration in relation to the calf muscle pump function. *Surgery*. 1989;106:829-835.
- Franzeck UK, Haselbach P, Speiser D, Bollinger A. Microangiopathy of cutaneous blood and lymphatic capillaries in chronic venous insufficiency (CVI). *Yale J Biol Med*. 1993;66:37-46.
- Browse NL, Burnand KG. The cause of venous ulceration. *Lancet*. 1982;2:243-245.
- Coleridge-Smith PD, Thomas P, Scurr JH, et al. Causes of venous ulceration: a new hypothesis. *Br Med J*. 1988;296:1726-1727.
- Falanga V, Eaglestein WH. The "trap" hypothesis of venous ulceration. *Lancet*. 1993;341:1006-1008.
- Eklöf B, Rutherford RB, Bergan JJ, et al. American Venous Forum International Ad Hoc Committee for Revision of the CEAP Classification. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg*. 2004;40:1248-1252.
- Jacob AG, Driscoll DJ, Shaughnessy WJ, et al. Klippel-Trénaunay syndrome: spectrum and management. *Mayo Clin Proc*. 1998;73:28-36.
- Kim J, Richards S, Kent PJ. Clinical examination of varicose veins—a validation study. *Ann R Coll Surg Engl*. 2000;82:171-175.
- Yao P, Mukhdomi T. Varicose vein endovenous laser therapy. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2021.
- Vasquez MA, Rabe E, McLafferty RB, et al. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. *J Vasc Surg*. 2010;52:1387-1396.
- Rutherford RB, Padberg FT Jr, Comerota AJ, et al. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg*. 2000;31:1307-1312.
- Fowler B, Zygmunt J, Ramirez H, Kolluri R. Venous insufficiency evaluation with duplex scanning. *J Vasc Ultrasound*. 2014;38(1):34-40.
- Labropoulos N, Tingson J, Pryor L, et al. Definition of venous reflux in lower extremity veins. *J Vasc Surg*. 2003;38:793-798.
- Labropoulos N, Kokkosis A, Spentzouris G, et al. The distribution and significance of varicosities in the saphenous trunks. *J Vasc Surg*. 2010;51:96-103.
- Zygmunt J, Pichot O, Dauplaise T. *Practical Phlebology: Venous Ultrasound*. London: CRC Press; 2013.
- Hirai M, Naiki K, Nakayama R. Chronic venous insufficiency in primary varicose veins evaluated by plethysmographic technique. *Angiology*. 1991;42:468-472.
- Criado E, Farber MA, Marston WA, et al. The role of air plethysmography in the diagnosis of chronic venous insufficiency. *J Vasc Surg*. 1998;27:660-670.
- Welkie JF, Comerota AJ, Kerr RP, et al. The hemodynamics of venous ulceration. *Ann Vasc Surg*. 1992;6:1-4.
- Belcaro G, Labropoulos N, Christopoulos D, et al. Noninvasive tests in venous insufficiency. *J Cardiovasc Surg (Torino)*. 1993;34:3-11.
- Harada RN, Katz ML, Comerota A. A noninvasive screening test to detect "critical" deep venous reflux. *J Vasc Surg*. 1995;22:532-537.
- Ibegbuna V, Delis KT, Nicolaides AN. Haemodynamic and clinical impact of superficial, deep and perforator vein incompetence. *Eur J Vasc Endovasc Surg*. 2006;31:535-541.
- Labropoulos N, Leon L, Kwon S, et al. Study of the venous reflux progression. *J Vasc Surg*. 2005;41:291-295.
- Ulukan MO, Karakaya A, Erkanli K, et al. Efficiency of prophylactic ablation of the tributary venous pathways draining around the saphenofemoral junction to decrease the rate of future varicose vein and symptoms occurrence. *Ann Vasc Surg*. 2021;75:267-274.
- Psaila JV, Melhuish J. Viscoelastic properties and collagen content of the long saphenous vein in normal and varicose veins. *Br J Surg*. 1989;76:37-40.
- Elsharawy MA, Naim MM, Abdelmaguid EM, et al. Role of saphenous vein wall in the pathogenesis of primary varicose veins. *Interact Cardiovasc Thorac Surg*. 2007;6:219-224.
- Labropoulos N, Giannoukas AD, Delis K, et al. Where does venous reflux start? *J Vasc Surg*. 1997;26:736-742.
- Caggiati A, Rosi C, Heyn R, et al. Age-related variations of varicose veins anatomy. *J Vasc Surg*. 2006;44:1291-1295.
- Somjen GM, Royle JP, Fell G, et al. Venous reflux patterns in the popliteal fossa. *J Cardiovasc Surg (Torino)*. 1992;33:85-91.
- Sales CM, Bilof ML, Petrillo KA, Luka NL. Correction of lower extremity deep venous incompetence by ablation of superficial venous reflux. *Ann Vasc Surg*. 1996;10:186-189.
- MacKenzie RK, Allan PL, Ruckley CV, et al. The effect of long saphenous vein stripping on deep venous reflux. *Eur J Vasc Endovasc Surg*. 2004;28:104-107.
- Nishibe T, Nishibe M, Akiyama S. Influence of superficial venous ablation on deep venous dilation and reflux in patients with saphenous varicose veins. *Vasc Endovascular Surg*. 2020;54(8):687-691.
- Mussa FF, Peden EK, Zhou W, et al. Iliac vein stenting for chronic venous insufficiency. *Tex Heart Inst J*. 2007;34:60-66.
- Sanford DA, Kelly D, Rhee SJ, et al. Importance of phasicity in detection of proximal iliac vein thrombosis with venous duplex examination. *J Vasc Ultrasound*. 2011;35:150-152.
- Felty CL, Rooke TW. Compression therapy for chronic venous insufficiency. *Semin Vasc Surg*. 2005;18:36-40.
- Kakkos SK, Daskalopoulou SS, Daskalopoulos ME, et al. Review on the value of graduated elastic compression stockings after deep vein thrombosis. *Thromb Haemost*. 2006;96:441-445.
- Marston W, Vowden K. Compression therapy: a guide to safe practice. In: *European Wound Management (EWMA) Position Document*. Understanding Compression Therapy. MEP Ltd; 2003:11-17.
- Mosti G, Cavezzi A, Bastiani L, Partsch H. Compression therapy is not contraindicated in diabetic patients with venous or mixed leg ulcer. *J Clin Med*. 2020;9(11):3709.
- World Union of Wound Healing Societies. *Principles of Best Practice: Compression in Venous Leg Ulcers*. A Consensus Document. MEP Ltd; 2008.
- Amsler F, Blättler W. Compression therapy for occupational leg symptoms and chronic venous disorders—a meta-analysis of randomised controlled trials. *Eur J Vasc Endovasc Surg*. 2008;35:366-372.

70. Couzan S, Leizorovicz A, Laporte S, et al. A randomized double-blind trial of upward progressive versus degressive compressive stockings in patients with moderate to severe chronic venous insufficiency. *J Vasc Surg*. 2012; 56:1344-1350.
71. Vuylsteke ME, Mordon SR. Endovenous laser ablation: a review of mechanisms of action. *Ann Vasc Surg*. 2012;26:424-433.
72. Viarengo LM, Viarengo G, Martins AM, Mancini MW, Lopes LA. Medium and long-term outcomes of endovenous treatment of varicose veins with a 1940 nm diode laser: critical analysis and technical considerations. *J Vasc Bras*. 2017;16:23-30.
73. Malskat WSJ, Poluektova AA, van der Geld CWM, et al. Endovenous laser ablation (EVLA): a review of mechanisms, modeling outcomes, and issues for debate. *Lasers Med Sci*. 2014;29:393-403.
74. Almeida J, Mackay E, Javier J, et al. Saphenous laser ablation at 1470 nm targets the vein wall, not blood. *Vasc Endovascular Surg*. 2009;43:467-472.
75. Schwarz T, Von Hohenberg E, Furtwängler C, et al. Endovenous laser ablation of varicose veins with the 1470-nm diode laser. *J Vasc Surg*. 2010;51: 1474-1478.
76. Mackay EG, Almeida JJ, Raines JK. Do different laser wavelengths translate into different patient experiences? *Endovasc Today*. 2006;45-48.
77. Timperman PE, Sichlau M, Ryu RK. Greater energy delivery improves treatment success of endovenous laser treatment of incompetent saphenous veins. *J Vasc Interv Radiol*. 2004;15:1061-1063.
78. Theivacumar NS, Dellagrammaticas D, Beale RJ, et al. Factors influencing the effectiveness of endovenous laser ablation (EVLA) in the treatment of great saphenous vein reflux. *Eur J Vasc Endovasc Surg*. 2008;35:119-123.
79. Pannier F, Rabe E, Maurins U. First results with a new 1470-nm diode laser for endovenous ablation of incompetent saphenous veins. *Phlebology*. 2009; 24:26-30.
80. Ferreira MB, do Nascimento Galego G, Nazário NO, et al. Use of 1,470 nm laser for treatment of superficial venous insufficiency. *J Vasc Bras*. 2021;20:e20200244.
81. Christenson JT, Gueddi S, Gemayel G, Bounameaux H. Prospective randomized trial comparing endovenous laser ablation and surgery for treatment of primary great saphenous varicose veins with a 2-year follow-up. *J Vasc Surg*. 2010;52:1234-1241.
82. Roth SM. Endovenous radiofrequency ablation of superficial and perforator veins. *Surg Clin North Am*. 2007;87:1267-1284.
83. Lurie F, Creton D, Eklof B, et al. Reprinted article "Prospective randomised study of endovenous radiofrequency obliteration (closure) versus ligation and vein stripping (EVOLVEs): two-year follow up." *Eur J Vasc Endovasc Surg*. 2011;42(suppl 1):S107-S113.
84. Rasmussen LH, Lawaetz M, Bjoern L, et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. *Br J Surg*. 2011;98:1079-1087.
85. Marsh P, Price BA, Holdstock J, et al. Deep Vein Thrombosis (DVT) after venous thermoablation techniques: rates of Endovenous Heat-induced Thrombosis (EHIT) and classical DVT after radiofrequency and endovenous laser ablation in a single centre. *Eur J Vasc Endovasc Surg*. 2010;40: 521-527.
86. Sadek M, Kabnick LS, Rockman CB, et al. Increasing ablation distance peripheral to the saphenofemoral junction may result in a diminished rate of endothermal heat-induced thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2013;1:257-262.
87. Kitagawa A, Yamada Y, Nagao T. The proximity of the superficial epigastric vein to the saphenofemoral junction is associated with endovenous heat-induced thrombosis after radiofrequency ablation for varicose veins. *J Vasc Surg Venous Lymphat Disord*. 2021;9(3):669-675.
88. Healy DA, Kimura S, Power D, et al. A systematic review and meta-analysis of thrombotic events following endovenous thermal ablation of the great saphenous vein. *Eur J Vasc Endovasc Surg*. 2018;56(3):410-424.
89. Borghese O, Pisani A, Di Centa I. Endovenous radiofrequency for chronic superficial venous insufficiency: clinical outcomes and impact in quality of life. *J Med Vasc*. 2021;46(1):3-8.
90. van den Bos RR, Milleret R, Neumann M, Nijsten T. Proof-of-principle study of steam ablation as novel thermal therapy for saphenous varicose veins. *J Vasc Surg*. 2011;53:181-186.
91. van Ruijven PW, van den Bos RR, Alazard LM, et al. Temperature measurements for dose-finding in steam ablation. *J Vasc Surg*. 2011;53:1454-1456.
92. Thomis S, Verbrugghe P, Milleret R, et al. Steam ablation versus radiofrequency and laser ablation: an in vivo histological comparative trial. *Eur J Vasc Endovasc Surg*. 2013;46:378-382.
93. Lislegaard Næs A-K, Halsteinli V, Seternes A. Steam ablation versus stripping of great saphenous varicose veins. *Tidsskr Nor Lægeforen*. 2019;139(5).
94. Pang KH, Bate GR, Darvall KA, et al. Healing and recurrence rates following ultrasound-guided foam sclerotherapy of superficial venous reflux in patients with chronic venous ulceration. *Eur J Vasc Endovasc Surg*. 2010;40:790-795.
95. Memetoglu ME, Yilmaz M, Kehlibar T. Ultrasonography-guided foam sclerotherapy in patients with small saphenous vein insufficiency. *J Vasc Surg Venous Lymphat Disord*. 2020;8(5):799-804.
96. Rathbun S, Norris A, Morrison N, et al. Performance of endovenous foam sclerotherapy in the USA for the treatment of venous disorders: ACP/SVM/AVF/SIR quality improvement guidelines. *Phlebology*. 2014;29:76-82.
97. Nael R, Rathbun S. Effectiveness of foam sclerotherapy for the treatment of varicose veins. *Vasc Med*. 2010;15:27-32.
98. Weiss RA, Sadick NS, Goldman MP, Weiss MA. Post-sclerotherapy compression: controlled comparative study of duration of compression and its effects on clinical outcome. *Dermatol Surg*. 1999;25:105-108.
99. Cartee TV, Wirth P, Greene A, et al. Ultrasound-guided foam sclerotherapy is safe and effective in the management of superficial venous insufficiency of the lower extremity. *J Vasc Surg Venous Lymphat Disord*. 2021;9(4):1031-1040.
100. Cavezzi A, Parsi K. Complications of foam sclerotherapy. *Phlebology*. 2012;27(suppl 1):46-51.
101. Peterson JD, Goldman MP. An investigation of side-effects and efficacy of foam-based sclerotherapy with carbon dioxide or room air in the treatment of reticular leg veins: a pilot study. *Phlebology*. 2012;27:73-76.
102. Peterson JD, Goldman MP, Weiss RA, et al. Treatment of reticular and telangiectatic leg veins: double-blind, prospective comparative trial of polidocanol and hypertonic saline. *Dermatol Surg*. 2012;38:1322-1330.
103. Guex J-J, Allaert F-A, Gillet J-L, et al. Immediate and midterm complications of sclerotherapy: report of a prospective multicenter registry of 12,173 sclerotherapy sessions. *Dermatol Surg*. 2005;31:123-128.
104. Parsi K. Paradoxical embolism, stroke and sclerotherapy. *Phlebology*. 2012; 27:147-167.
105. Parsons ME. Sclerotherapy basics. *Dermatol Clin*. 2004;22:501-508.
106. Kern P, Ramelet A-A, Wutschert R, et al. Single-blind, randomized study comparing chromated glycerin, polidocanol solution, and polidocanol foam for treatment of telangiectatic leg veins. *Dermatol Surg*. 2004;30:367-372.
107. Brodersen JP, Geismar U. Catheter-assisted vein sclerotherapy: a new approach for sclerotherapy of the greater saphenous vein with a double-lumen balloon catheter. *Dermatol Surg*. 2007;33:469-475.
108. Van Eekeren RRJP, Boersma D, Elias S, et al. Endovenous mechanochemical ablation of great saphenous vein incompetence using the ClariVein device: a safety study. *J Endovasc Ther*. 2011;18:328-334.
109. Elias S, Raines JK. Mechanochemical tumescentless endovenous ablation: final results of the initial clinical trial. *Phlebology*. 2012;27:67-72.
110. Boersma D, van Eekeren RRJP, Werson DAB, et al. Mechanochemical endovenous ablation of small saphenous vein insufficiency using the ClariVein® Device: one-year results of a prospective series. *Eur J Vasc Endovasc Surg*. 2013;45:299-303.
111. Mohamed AH, Leung C, Wallace T. A randomized controlled trial of endovenous laser ablation versus mechanochemical ablation with ClariVein in the Management of Superficial Venous Incompetence (LAMA trial). *Ann Surg*. 2021;273(6):e188-e195.
112. Wang YM, Cheng LF, Li N. Histopathological study of vascular changes after intra-arterial and intravenous injection of N-butyl-2-cyanoacrylate. *Chin J Dig Dis*. 2006;7:175-179.
113. Almeida J, et al. *Cyanoacrylate Glue Great Saphenous Vein Ablation: Preliminary 180-Day Follow-Up of a First-In-Man Feasibility Study of a No-Compression-No-Local-Anesthesia Technique*. Presented at the American Venous Forum 24th Annual Congress. Orlando, FL; 2012.
114. O'Banion LA, Reynolds KB, Kochubey M, et al. Treatment of superficial venous reflux in CEAP 6 patients: a comparison of cyanoacrylate glue and radiofrequency ablation techniques. *J Vasc Surg Venous Lymphat Disord*. 2021;9(5):1215-1221.
115. Morrison N, Gibson K, Vasquez M. Five-year extension study of patients from a randomized clinical trial (VeClose) comparing cyanoacrylate closure versus radiofrequency ablation for the treatment of incompetent great saphenous veins. *J Vasc Surg Venous Lymphat Disord*. 2020;8(6):978-989.
116. Gibson K, Minjarez R, Rinehardt E, Ferris B. Frequency and severity of hypersensitivity reactions in patients after VenaSeal™ cyanoacrylate treatment of superficial venous insufficiency. *Phlebology*. 2020;35(5):337-344.
117. Olivencia JA. Complications of ambulatory phlebectomy: review of 1000 consecutive cases. *Dermatol Surg*. 1997;23:51-54.
118. Kabnick LS, Ombrellino M. Ambulatory phlebectomy. *Semin Intervent Radiol*. 2005;22:218-224.
119. Rasmussen LH, Bjoern L, Lawaetz M, et al. Randomised clinical trial comparing endovenous laser ablation with stripping of the great saphenous vein: clinical outcome and recurrence after 2 years. *Eur J Vasc Endovasc Surg*. 2010;39:630-635.
120. Biemans AA, Kockaert M, Akkersdijk GP, et al. Comparing endovenous laser ablation, foam sclerotherapy and conventional surgery for great saphenous varicose veins. *J Vasc Surg*. 2013;58:727-734.
121. Lurie F, Creton D, Eklof B, et al. Prospective randomized study of endovenous radiofrequency obliteration (closure procedure) versus ligation and stripping in a selected patient population (EVOLVEs Study). *J Vasc Surg*. 2003;38:207-214.
122. Winterborn RJ, Foy C, Earnshaw JJ. Causes of varicose vein recurrence: late results of a randomized controlled trial of stripping the long saphenous vein. *J Vasc Surg*. 2004;40:634-639.
123. Perrin M, Ramelet AA. Pharmacological treatment of primary chronic venous disease: rationale, results and unanswered questions. *Eur J Vasc Endovasc Surg*. 2011;41:117-125.
124. Casley-Smith JR, Morgan RG, Piller NB. Treatment of lymphedema of the arms and legs with 5,6-Benzo- α -pyrone. *N Engl J Med*. 1993;329:1158-1163.
125. Casley-Smith JR, Gaffney RM. Excess plasma proteins as a cause of chronic inflammation and lymphoedema: quantitative electron microscopy. *J Pathol*. 1981;133:243-272.
126. Katsenis K. Micronized purified flavonoid fraction (MPFF): a review of its pharmacological effects, therapeutic efficacy, and benefits in the management of chronic venous insufficiency. *Curr Vasc Pharmacol*. 2005;3:1-9.
127. Petruzzellis V, Troccoli T, Candiani C, et al. Oxerutins (Venoruton): efficacy in chronic venous insufficiency—a double-blind, randomized, controlled study. *Angiology*. 2002;53:257-263.
128. Diehm C, Vollbrecht D, Amendt K, Comberg H. Medical edema protection—clinical benefit in patients with chronic deep vein incompetence. A placebo controlled double blind study. *Vasa*. 1992;21:188-192.

129. Diehm C, Trampisch HJ, Lange S, Schmidt C. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. *Lancet*. 1996;347:292-294.
130. Ramelet A-A, Daflon 500 mg: symptoms and edema clinical update. *Angiology*. 2005;56(suppl 1):S25-S32.
131. Tejerina T, Ruiz E. Calcium dobesilate: pharmacology and future approaches. *Gen Pharmacol*. 1998;31:357-360.
132. Ciapponi A, Laffaire E, Roqué M. Calcium dobesilate for chronic venous insufficiency: a systematic review. *Angiology*. 2004;55:147-154.
133. Martínez-Zapata MJ, Moreno RM, Gich I, Urrútia G, Bonfill X, Chronic Venous Insufficiency Study Group. A randomized, double-blind multicentre clinical trial comparing the efficacy of calcium dobesilate with placebo in the treatment of chronic venous disease. *Eur J Vasc Endovasc Surg*. 2008;35(3):358-365.
134. Vayssairat M. Placebo-controlled trial of naftazone in women with primary uncomplicated symptomatic varicose veins. *Phlebology*. 1997;12:17-20.
135. Callam MJ. Prevalence of chronic leg ulceration and severe chronic venous disease in western countries. *Phlebology*. 1992;7(suppl 1):6-12.
136. Heit JA, Rooke TW, Silverstein MD, et al. Trends in the incidence of venous stasis syndrome and venous ulcer: a 25-year population-based study. *J Vasc Surg*. 2001;33:1022-1027.
137. Gohel MS, Heatley F, Liu X. Early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration: the EVRA RCT. *Health Technol Assess*. 2019;23(24):1-96.
138. Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. *Lancet*. 2004;363:1854-1859.
139. Zamboni P, Cisno C, Marchetti F, et al. Minimally invasive surgical management of primary venous ulcers vs. compression treatment: a randomized clinical trial. *Eur J Vasc Endovasc Surg*. 2003;25:313-318.
140. Pierik EG, van Urk H, Hop WC, Wittens CH. Endoscopic versus open subfascial division of incompetent perforating veins in the treatment of leg ulceration: a randomized trial. *J Vasc Surg*. 1997;26:1049-1054.
141. O'Donnell TF. The role of perforators in chronic venous insufficiency. *Phlebology*. 2010;25:3-10.
142. Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg*. 2011;53(5 suppl):2S-48S.
143. Bello M, Scriven M, Hartshorne T, et al. Role of superficial venous surgery in the treatment of venous ulceration. *Br J Surg*. 1999;86:755-759.
144. Marrocco CJ, Atkins MD, Bohannon WT, et al. Endovenous ablation for the treatment of chronic venous insufficiency and venous ulcerations. *World J Surg*. 2010;34:2299-2304.
145. Goldschmidt E, Schafer K, Lurie F. A systematic review on the treatment of nonhealing venous ulcers following successful elimination of superficial venous reflux. *J Vasc Surg. Venous Lymphat Disord*. 2021;9(4):1071-1076.e1.
146. Lawrence PF, Alktaifi A, Rigberg D, et al. Endovenous ablation of incompetent perforating veins is effective treatment for recalcitrant venous ulcers. *J Vasc Surg*. 2011;54:737-742.
147. Marsh P, Price BA, Holdstock JM, Whiteley MS. One-year outcomes of radiofrequency ablation of incompetent perforator veins using the radiofrequency stylet device. *Phlebology*. 2010;25:79-84.
148. Proebstle TM, Herdemann S. Early results and feasibility of incompetent perforator vein ablation by endovenous laser treatment. *Dermatol Surg*. 2007;33:162-168.
149. Elias S, Peden E. Ultrasound-guided percutaneous ablation for the treatment of perforating vein incompetence. *Vascular*. 2007;15:281-289.
150. Hingorani AP, Ascher E, Marks N, et al. Predictive factors of success following radio-frequency stylet (RFS) ablation of incompetent perforating veins (IPV). *J Vasc Surg*. 2009;50:844-848.
151. Raju S, Darcey R, Neglén P. Unexpected major role for venous stenting in deep reflux disease. *J Vasc Surg*. 2010;51:401-408.
152. Yang X, Wu X, Peng Z, et al. Outcomes of endovenous laser ablation with additional iliac vein stenting of nonthrombotic lesions in patients presenting with active venous ulcers. *J Vasc Surg Venous Lymphat Disord*. 2021;9(6):1517-1525.
153. Kistner RL. Surgical repair of the incompetent femoral vein valve. *Arch Surg*. 1975;110:1336-1342.
154. Raju S, Berry MA, Neglén P. Transcommissural valvuloplasty: technique and results. *J Vasc Surg*. 2000;32:969-976.
155. Kistner RL, Masuda E, Lurie F. Valvuloplasty in primary venous insufficiency. In: Bergan JJ, Bunke-Paquette N, eds. *The Vein Book*. 2nd ed. New York: Oxford University Press; 2014:486-498.
156. Neglén P, Raju S. Venous reflux repair with cryopreserved vein valves. *J Vasc Surg*. 2003;37:552-557.
157. Maleti O, Perrin M. Reconstructive surgery for deep vein reflux in the lower limbs: techniques, results and indications. *Eur J Vasc Endovasc Surg*. 2011;41:837-848.
158. Lugli M, Guerzoni S, Garofalo M, et al. Neovalve construction in deep venous incompetence. *J Vasc Surg*. 2009;49:156-162.
159. Dalsing MC. Prosthetic venous valves. In: Bergan JJ, Bunke-Paquette N, eds. *The Vein Book*. 2nd ed. New York: Oxford University Press; 2014:499-504.
160. Ofenloch JC, Chen C, Hughes JD, Lumsden AB. Endoscopic venous valve transplantation with a valve-stent device. *Ann Vasc Surg*. 1997;11:62-67.
161. Pavcnik D, Yin Q, Uchida B, et al. Percutaneous autologous venous valve transplantation: short-term feasibility study in an ovine model. *J Vasc Surg*. 2007;46:338-345.
162. Phillips MN, Dijkstra ML, Khin NY, Lane RJ. Endovenous valve transfer for chronic deep venous insufficiency. *Eur J Vasc Endovasc Surg*. 2013;46:360-365.
163. Boudjemline Y, Bonnet D, Sidi D, Bonhoeffer P. Is percutaneous implantation of a bovine venous valve in the inferior vena cava a reliable technique to treat chronic venous insufficiency syndrome? *Med Sci Monit*. 2004;10:BR61-BR66.
164. Moriyama M, Kubota S, Tashiro H, Tonami H. Evaluation of prosthetic venous valves, fabricated by electrospinning, for percutaneous treatment of chronic venous insufficiency. *J Artif Organs*. 2011;14:294-300.
165. Weber B, Robert J, Ksiazek A, et al. Living-engineered valves for transcatheter venous valve repair. *Tissue Eng Part C Methods*. 2014;20(6):451-463.
166. Jones CM, Hinds MT, Pavcnik D. Retention of an autologous endothelial layer on a bioprosthetic valve for the treatment of chronic deep venous insufficiency. *J Vasc Interv Radiol*. 2012;23:697-703.
167. Levi DS, Kusnezov N, Carman GP. Smart materials applications for pediatric cardiovascular devices. *Pediatr Res*. 2008;63:552-558.
168. de Borst GJ, Moll FL. Percutaneous venous valve designs for treatment of deep venous insufficiency. *J Endovasc Ther*. 2012;19:291-302.
169. Yavuz T, Acar AN, Yavuz K, Ekingen E. A retrospective study of deep vein insufficiency treatment device: ICT. *Ann Vasc Dis*. 2020;13(3):255-260.

**INTRODUCTION, 513****EPIDEMIOLOGY AND PREVALENCE OF STAGE V KIDNEY DISEASE, 513**

Survival, 513
Hemodialysis, 513

VASCULAR ANATOMY, 513

Nomenclature, 513
Autogenous Arteriovenous Accesses, 514
Prosthetic Arteriovenous Accesses, 514
Anatomic Variants, 514

PATHOGENESIS OF ACCESS FAILURE, 515

Failure to Mature, 515

Stenosis Development in Mature Accesses,
with or without Thrombosis, 515

DIAGNOSTIC EVALUATION, 515

Monitoring, 515
Surveillance, 515
Diagnostic Testing, 515

CATHETER-BASED TREATMENT OF FAILING ACCESSSES, 516

Interventions for Non-Thrombosed
Accesses, 516
Four-Step Procedure for Thrombosed
Accesses, 516

OUTCOMES, 518

Success Rates, 518
Complications, 518

NEWER APPROACHES, 519

Stent Grafts, 519
Interventional Nephrology, 519
Preemptive Angiography, 519
Salvage of Hypoplastic Fistulas, 519

SUMMARY, 519**INTRODUCTION**

Interventional cardiologists play an important role in the lives of patients with end-stage kidney disease (ESKD) by salvaging hemodialysis accesses that develop venous stenoses or undergo thrombosis. Although interventional nephrologists perform the majority of routine access angiographic procedures, interventional cardiologists frequently perform urgent or emergent procedures that fall outside the schedule of an outpatient interventional nephrology laboratory to ensure that patients with ESKD will not miss a hemodialysis session or need a temporary catheter. This chapter describes the pathophysiology of hemodialysis access failure, reviews the success rates for endovascular treatments, and uses color figures and videos to illustrate the catheter-based approaches used by interventional cardiologists to treat failing and thrombosed fistulas and grafts.

EPIDEMIOLOGY AND PREVALENCE OF STAGE V KIDNEY DISEASE**Survival**

Approximately 2 in every 1,000 persons in the United States have ESKD, and more than 80% undergo hemodialysis.¹ In 2017, 124,500 new patients registered for hemodialysis, raising the total number of patients with ESKD undergoing renal replacement therapy (RRT) to 678,383.¹ In 2014, the annual mortality rate for patients on hemodialysis was 16%,² which reflected an improvement in the mortality rate of 24% that existed in 2002.³

The growing prevalence of ESKD has been attributed to the undertreatment of patients with hypertension and the growing incidence of diabetes. Even though the ESKD population constitutes less than 1% of the total Medicare

population, total costs for RRT account for about 7% of Medicare spending.¹

Hemodialysis

The creation of hemodialysis fistulas and grafts is one of the most common types of vascular surgery in the United States, accounting for 40% to 50% of the operative volume in some programs.⁴ Functioning arteriovenous fistulas (AVFs) and arteriovenous grafts (AVGs) are the lifeline for patients with ESKD.

Hemodialysis AVFs and AVGs have limited patency. AVFs generally have longer patencies than AVGs but are not feasible for every patient. Accordingly, the “fistula first” policy of 2006⁵ has been supplanted by a patient-centered approach that creates an individualized life plan to individualize hemodialysis access in response to changing circumstances for each patient.⁶

VASCULAR ANATOMY**Nomenclature**

An AVF is surgically created when an artery is directly anastomosed to an autogenous vein. An AVG is created when a segment of a prosthetic material such as polytetrafluoroethylene (PTFE) connects a native artery with a vein.

Common modes of failure for hemodialysis AVFs and AVGs include the early appearance of a stenosis at the inflow arteriovenous (AV) anastomosis or the late development of an outflow stenosis in the venous limb (Table 28.1). As the stenosis worsens, flow is reduced, and thrombosis may ensue. Thrombosed and nonthrombosed AVFs and AVGs are amenable to treatment with catheter-based approaches,⁷ which can promptly restore the usability of the access and have the added advantage over surgical

TABLE 28.1 Modes of Access Failure

Primary failure of new fistulas
Inflow (anastomotic) stenosis
Failure to undergo hypertrophy
Failure of old fistulas and grafts
Isolated venous or outflow anastomotic stenosis
Thrombosis

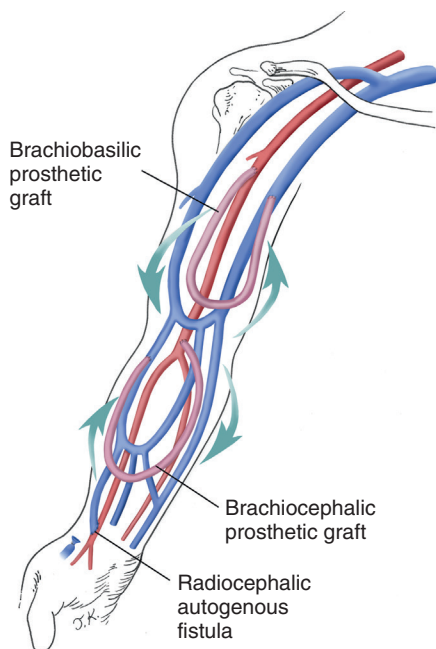


FIGURE 28.1 Access anatomy of the upper extremity. A radial-cephalic fistula (*small distal arrows*) is created by an end-to-side anastomosis between the cephalic vein and the radial artery. The distal stump of the cephalic vein is ligated. A brachial-cephalic graft in the forearm (*large arrows*) requires the surgical placement of a polytetrafluoroethylene (PTFE) loop using end-to-side connections. A brachial-basilic graft in the upper arm (*larger arrows*) requires the surgical insertion of a PTFE loop using end-to-side connections. (Reprinted with permission from the author and Elsevier Inc.²¹)

techniques of saving venous conduit for future accesses and thereby prolonging survival on hemodialysis.

Autogenous Arteriovenous Accesses

A fistula is surgically created when a native inflow artery is directly anastomosed with a native outflow vein. A common configuration at the wrist involves an end-to-side anastomosis between the radial artery and the cephalic vein, creating the Brescia-Cimino radial-cephalic fistula (Figure 28.1). Another common configuration in the upper arm entails mobilization and tunneling of the basilic vein laterally and superficially for an end-to-side anastomosis with the brachial artery, creating a transposed brachial-basilic fistula.

Prosthetic Arteriovenous Accesses

A prosthetic AV access is constructed by surgically interposing a segment of PTFE between an artery and a vein in either a straight or looped configuration. Loop grafts are favored over straight grafts because they increase the length of the graft amenable to needle entry. The most common graft patterns include the brachial-cephalic configuration in the

forearm and the brachial-basilic configuration in the upper arm (see Figure 28.1).

In the forearm, the radial-cephalic autogenous access and the brachial-cephalic prosthetic access are the favored configurations, in which the outflow in both instances traverses the cephalic vein. This follows a medial-to-lateral course, continues along the lateral aspect of the arm, traverses the pectoral groove, and anastomoses with the axillary vein and then becomes the subclavian vein.

In the upper arm, the brachial-basilic autogenous access and the brachial-basilic prosthetic graft are common configurations, in which the outflow in both instances traverses the basilic vein. This follows a lateral-to-medial course and continues in a straight line into the axillary vein, subclavian vein, and thence into the central circulation (see Figure 28.1).

Anatomic Variants

Alternative patterns for prosthetic grafts include the brachial-basilic graft in the forearm that has a lateral-to-medial course and the brachial-cephalic graft in the upper arm that has a medial-to-lateral course.

Another configuration in the forearm consists of the proximal radial artery anastomosed in a side-to-side manner with the median antebrachial vein, producing a double-outlet configuration coursing proximally and distally from the AV anastomosis. Another type of “double-outlet” access is the radial-cephalic fistula that drains as well into the basilic vein, a desirable variant that reduces the risk of thrombosis when one limb develops an outflow stenosis.

In the thigh, the superficial femoral artery-greater saphenous vein configuration is preferred, with venous outflow following a lateral-to-medial course (Figure 28.2).

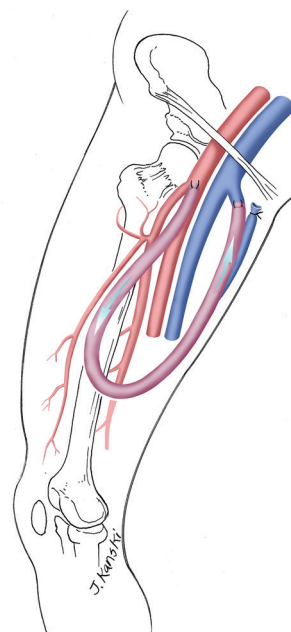


FIGURE 28.2 Access anatomy of the thigh. Creation of a thigh graft involves the surgical placement of a polytetrafluoroethylene (PTFE) loop connected end-to-side with superficial femoral artery and end-to-end with the greater saphenous vein. (Reprinted by permission from the author and Elsevier.²¹)

PATHOGENESIS OF ACCESS FAILURE

An AVF has a greater chance for long-term patency than an AVG, but the primary patency of fistulas remains low because of the lack of suitable anatomy in many cases and the inability to achieve adequate hypertrophy. Fewer than 50% of fistulas mature adequately to allow reliable hemodialysis.^{8,9} When fistulas mature adequately and have been successfully used for hemodialysis, they fail after a median of 3 to 7 years.¹⁰ Patients who are not candidates for fistulas can have prosthetic grafts constructed from PTFE. Although the primary patency of such prosthetic grafts exceeds 80%,⁴ prosthetic accesses fail after a median lifetime of only 12 to 18 months.¹⁰

The two modes of failure commonly affecting AVFs and AVGs, whether it is the early development of a stenosis at the AV anastomosis or the late development of an outflow stenosis in the venous limb, are both amenable to interventional treatment (see Table 28.1).

Failure to Mature

The presence of an inflow stenosis obstructs flow, limits pressurization, and restricts flow-mediated hypertrophy.^{11,12} This is more common in patients with diabetes and in older patients. Histologic studies suggest that neointimal hyperplasia at the juxtaanastomotic site is the cause of the inflow stenosis.¹³ After successful angioplasty, the primary signal for flow-induced remodeling and dilatation is believed to be increased shear stress.¹²

Stenosis Development in Mature Accesses, with or without Thrombosis

In mature hemodialysis accesses, high pressures and flow in the thin-walled outflow vein of either an AVF or an AVG generate high shear stress and trigger fibromuscular hyperplasia.¹³ When the hyperplasia is excessive, a severe stenosis develops, reduces flow, and may cause thrombosis. Stenoses can occur anywhere in AVGs, but in approximately half of cases, the stenosis occurs at the anastomosis between the prosthetic AVG and the outflow vein.^{14,15} Other sites of stenosis formation include a nonanastomotic location within a peripheral outflow vein, the AVG itself, central veins, or multiple locations.^{14,15} Although AVFs technically have no outflow anastomosis, they are susceptible to stenosis formation in the “arterialized” outflow vein.

When a severe stenosis develops, stasis may ensue and cause thrombosis. Most thrombus that occurs secondarily within an access is red thrombus, which is rich in fibrin and red blood cells and easily extracted with rheolytic methods. The platelet-rich white clot at the arterial inflow anastomosis is usually resistant to rheolytic or thrombolytic methods and may require mechanical removal with a Fogarty embolectomy catheter (Edwards Lifesciences).

Primary thrombosis of mature hemodialysis accesses occurs rarely. It may be associated with hypercoagulable states associated with coronavirus infection,¹⁶ myocardial infarction, major surgery, or sepsis. When primary thrombosis of an access occurs without an identifiable pathogenetic stenosis or in the setting of a chronic hypercoagulable

state such as Factor V Leiden or the antiphospholipid syndrome, chronic oral anticoagulation is recommended.

DIAGNOSTIC EVALUATION

The National Kidney Foundation-Dialysis Outcomes Quality Initiative document recommends an organized program to identify failing fistulas and grafts.¹⁷

Monitoring

The patient's history may provide clues about the location of an inflow or outflow obstruction. Failure of a new AVF to develop suggests the presence of an inflow stenosis. Increased postdialysis bleeding suggests the development of an outflow stenosis.

The physical examination may reveal the site of access stenosis. A continuous medium-pitched bruit and a prominent thrill along the length of a ballotable access are the hallmarks of a normal access. A soft bruit and complete absence of a thrill suggest the presence of an inflow stenosis. A prominent pulsation and a short, high-pitched bruit are signs of outflow obstruction. Multiple aneurysmal segments in the distribution of a mega-access may reflect the presence of high pressure caused by an outflow stenosis. Severe arm edema usually indicates dual venous obstruction (cephalic and basilic) or a central stenosis or occlusion.

Surveillance

Surveillance denotes the performance of noninvasive testing of access structure and function. Measurements of intra-access flow and static venous dialysis pressures can provide clues about access adequacy. Rising pressures of more than 150 mm Hg at a constant flow of 200 mL/min on hemodialysis may indicate the presence of an outflow stenosis. Estimating the recirculation fraction using urea concentrations or clinical parameters such as body weight, volume status, or serum potassium concentration may indicate incomplete dialysis. These are probably relatively late predictors of hemodialysis access failure and become abnormal at the time of impending thrombosis.

Diagnostic Testing

An angiogram (i.e., fistulogram) is indicated when hemodialysis cannot be successfully carried out or thrombosis is imminent (Table 28.2). Physical signs of imminent thrombosis include diminution or disappearance of a bruit or a change from a continuous medium-pitched bruit to a short high-pitched bruit. Thrombosis may be imminent when there is difficulty accessing the AVF or AVG; access-needle thrombosis; decreased dialysis efficiency or increased dialysis time, increasing pressure in return line at constant flow; or increased recirculation fraction to greater than 20%. The development of arm edema or a pseudoaneurysm is another indication for a fistulogram.

Mild erythema over an access without tenderness or edema is usually not a sign of infection, which instead is usually characterized by cellulitis, fluctuance, skin breakdown,

TABLE 28.2 Indications for Invasive Evaluation of Failing or Thrombosed Dialysis Accesses

Delayed maturation of hypoplastic fistula
Access thrombosis
Increased postdialysis bleeding
Absent or decreased thrill
Absent bruit or pulse
Change in bruit from a continuous medium pitch to a short high pitch
New prominent pulsation over access
Pseudoaneurysm
Recurrent access needle thrombosis
Repeated difficulty initiating hemodialysis
Decreased dialysis efficiency
Increased dialysis time
Increasing pressure in return line at constant flow
Peripheral edema in graft extremity
Increased recirculation fraction >20%

TABLE 28.3 Contraindications to Endovascular Treatment of Thrombosed Dialysis Accesses

Right-to-left intracardiac shunt
Pulmonary hypertension
Infected access
Recent surgical revision (within ~30 days)

or purulent discharge, although it should be noted that uremia may mask the usual systemic signs of infection such as fever and leukocytosis. The presence of access infection is a contraindication to catheter-based treatments (Table 28.3).

Patients with malfunctioning accesses who have not missed a hemodialysis session can be scheduled urgently for a fistulogram on their next day off from hemodialysis, but patients with access thrombosis require attention within 1 day to avoid using temporary catheters or missing a dialysis session.⁷

Before performing a fistulogram, an operator should note the etiology of ESKD, concurrent illnesses, access history, medications, and indications or contraindications. Neither warfarin nor the new direct-acting oral anticoagulants should be discontinued before performing a fistulogram.

Physical examination focuses on the access site and entails a general evaluation of volume status by assessing vital signs, weight change, jugular venous pressure, and lung and cardiac findings. The serum potassium level should be measured if a dialysis session has been missed. An intravenous line for administering light procedural sedation should be placed in a vein unlikely to be needed for future access creation. Ipsilateral hand veins are permissible.

Many physicians administer aspirin 325 mg orally before the procedure, but this can be omitted or replaced with clopidogrel in patients who are allergic to aspirin. Patients are often pretreated with diphenhydramine 50 mg orally. Because catheter-based procedures are performed using light sedation using low doses of fentanyl and midazolam, there is no requirement for fasting.¹⁸ Local anesthesia is achieved with 2% lidocaine. Heparin is not needed for patient AVFs and AVGs because flow is high, and procedures are performed quickly. If there is access thrombosis, however, many interventionalists give heparin 5000 U intravenously. Antibiotic prophylaxis with cephalothin 1 g intravenously is commonly used. If there is a cephalosporin allergy, 1 g of vancomycin over 1 hour can be substituted.

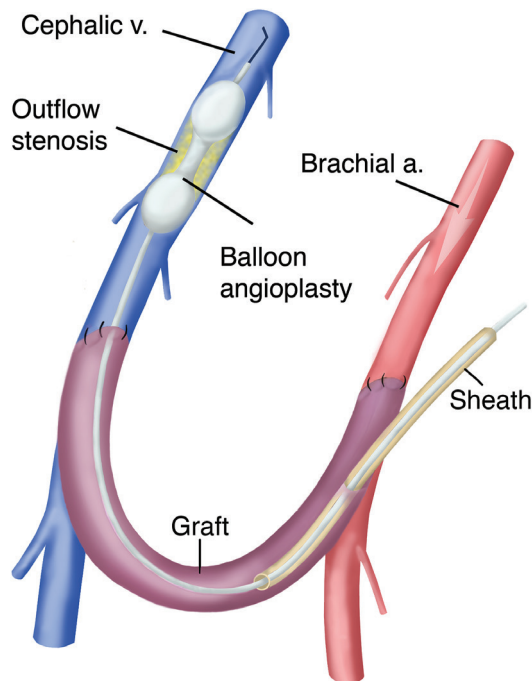


FIGURE 28.3 Balloon angioplasty of a stenosis in the venous limb of a prosthetic hemodialysis access. a, Artery; v, vein. (Reprinted by permission from the author and Elsevier.⁷)

CATHETER-BASED TREATMENT OF FAILING ACCESSSES

Interventions for Non-Thrombosed Accesses

Catheter-based therapy of malfunctioning non-thrombosed AVFs and AVGs is straightforward. A diagnostic fistulogram is first obtained through a 4-Fr Micropuncture access set (Cook) directed toward the inflow if the AVF is hypoplastic or directed toward the outflow if there is suspicion of an outflow stenosis. When a stenosis is identified, angioplasty can be carried out through a 4-Fr sheath using coronary angioplasty balloons or through 4- or 5-Fr sheaths using peripheral monorail balloons (Sterling, Boston Scientific Medi-Tech). If ultrahigh-pressure balloons are needed, a 6-Fr sheath may be placed to accommodate high-pressure balloons (Dorado, Bard Peripheral) (Figure 28.3). One study found that paclitaxel-coated balloons conferred no benefit over conventional balloons in reducing restenosis,¹⁹ but another randomized trial suggested that using IN.PACT™ paclitaxel-coated balloons (Medtronic) resulted in higher primary patency rates (83% vs 60%) without an increase in access thrombosis compared with using conventional balloons.²⁰ After the procedure, hemostasis can be achieved by placing a 3-0 monofilament nylon suture that can be removed 1 hour to 1 day later.

Four-Step Procedure for Thrombosed Accesses (Table 28.4)

The treatment of patients with thrombosed AVFs and AVGs is also straightforward but requires a multistep procedure performed at a single sitting.²¹ After local anesthetic is administered, the thrombosed AVF or AVG is entered in

TABLE 28.4 Four-Step Approach for Thrombosed Accesses

1. Thrombectomy of outflow and inflow segments
2. Percutaneous transluminal angioplasty of venous outflow stenosis
3. Fogarty thrombectomy of adherent clot at the arterial inflow anastomosis
4. Angiography of central veins

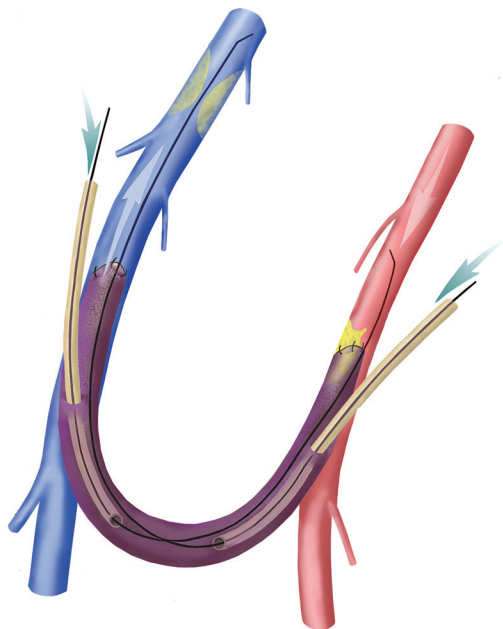


FIGURE 28.4 Cross-sheath method. A 6-Fr sheath is inserted into the access near the arterial inflow anastomosis and directed into the direction of the outflow, and a 6-Fr sheath is inserted into the access near the venous outflow in the direction of the inflow. Guidewires are advanced in the direction of the inflow and outflow under fluoroscopic guidance. No contrast is injected into a thrombosed access. (Reprinted with permission from the author and Elsevier Inc.²¹)

both the inflow and the outflow directions with a percutaneous 18-gauge needle or a 4-Fr Micropuncture access set (Cook) without using contrast. Free movement of the guidewire is evidence that intraluminal entry has been successful, which can be followed by placement of two 6-Fr sheaths, with sheath tips facing but not overlapping each other (Figure 28.4). Two 150-cm 0.018-in V-18 hydrophilic control wires (Boston Scientific Medi-Tech) can be advanced under fluoroscopic guidance without contrast injection.

Thrombectomy

The first step entails declotting. A device such as the AVX rheolytic thrombectomy catheter (AngioJet, Possis Medical) or the Indigo system (Penumbra) is advanced first in the outflow direction (Figure 28.5) and then in the inflow direction (Figure 28.6). After flow is achieved, the access and the sheaths are flushed with saline, and angiography is performed to identify the culprit stenosis.

Angioplasty, Stenting, or Stent Grafting of Stenosis

The second step in treating a thrombosed access entails angioplasty of the culprit stenosis with 4- to 10-mm balloons (Figure 28.7). The venous stenosis may require dilation pressures greater than 20 atm with high-pressure, noncompliant

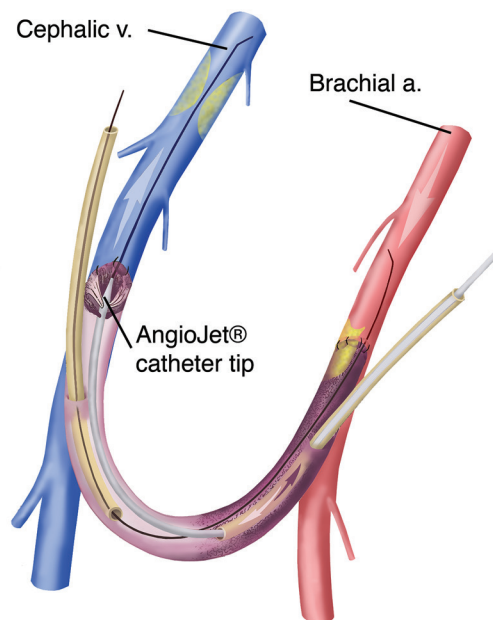


FIGURE 28.5 Rheolytic thrombectomy of venous outflow. a, Artery; v, vein. (Reprinted with permission from the author and Elsevier Inc.²¹)

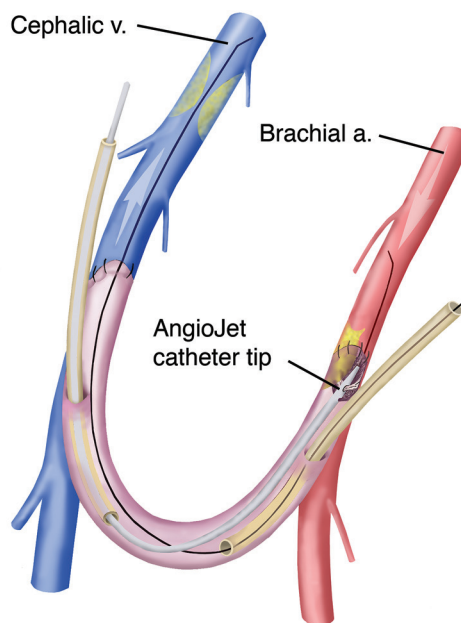


FIGURE 28.6 Rheolytic thrombectomy of arterial inflow. a, Artery; v, vein. (Reprinted with permission from the author and Elsevier Inc.²¹)

balloons, such as the Dorado balloon (Bard). Peripheral cutting balloons should be used cautiously because they increase the risk of perforation.²² Although stents are usually reserved for severe recoil, venous perforations, or recurrent stenoses, the use of a Fluency Plus Endovascular Stent (Bard Peripheral)²³ or a Viabahn Endoprosthesis (WL Gore and Associates)^{24,25} may reduce restenosis.

Fogarty Embolectomy

The third step in treating patients with thrombosed access involves treating the inflow stenosis. Most patients require mechanical embolectomy to remove the resistant white

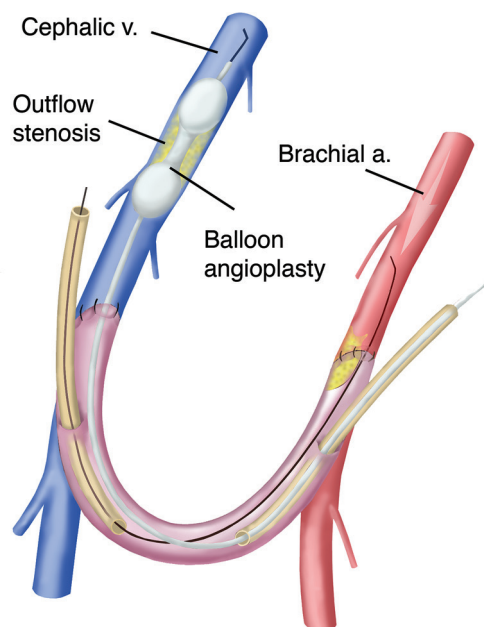


FIGURE 28.7 Balloon dilatation of outflow stenosis. The outflow stenosis is commonly found at or near the venous outflow anastomosis but can be encountered anywhere in the peripheral vein (v). a, Artery. (Reprinted with permission from the author and Elsevier Inc.²¹)

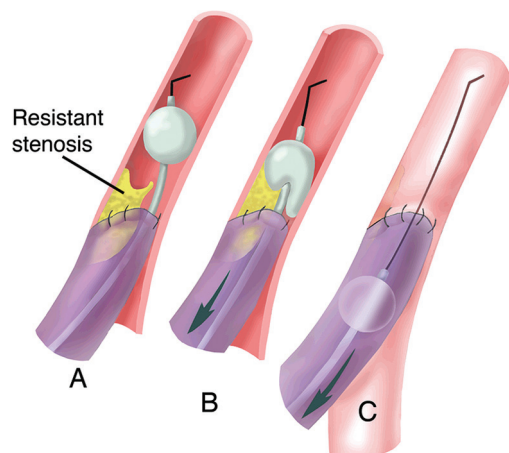


FIGURE 28.8 Fogarty embolectomy. The balloon catheter is inflated (A), pulled back to the thrombus (B), and forcefully withdrawn to mechanically dislodge the resistant inflow stenosis (C). (Reprinted with permission from the author and Elsevier Inc.²¹)

platelet-rich thrombus at the arterial inflow (Figure. 28.8), using an over-the-wire Fogarty Thru-Lumen Embolectomy Catheter (Edwards Lifesciences). The macerated thrombus can then be extracted by using rheolytic thrombectomy. In some cases, there are “balanced” inflow and outflow stenoses, both of which required ultrahigh-pressure balloon angioplasty.

Central Venous Angiography

The fourth step entails venography of the entire venous outflow and central veins to exclude the presence of a central venous stenosis (Figure 28.9), which is commonly caused by prior catheter placement or pacemaker or defibrillator leads. Treatment of a central vein stenosis requires large-diameter devices such the XXL balloon (Boston Scientific Medi-Tech),

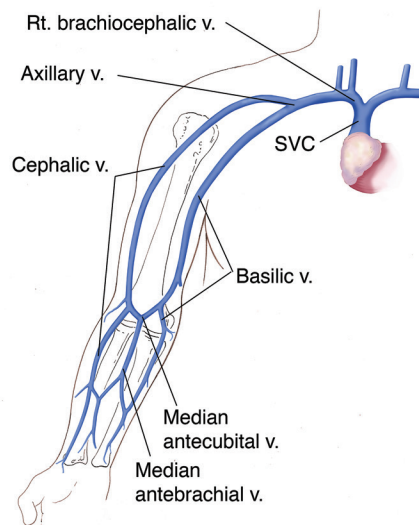


FIGURE 28.9 Central and peripheral venous anatomy. a, Artery; Rt, right; SVC, superior vena cava; v, vein. (Reprinted with permission from the author and Elsevier.²¹)

Atlas balloon (Bard) or SMART Control stent (Cordis). Pre-emptive treatment of asymptomatic central vein stenoses is of uncertain benefit.²⁶

Video Demonstration

The four-step approach for treating thrombosed access can be reviewed from a series of videos. Thrombectomy is first carried out in the outflow (Video 28.1) and inflow directions (Video 28.2). After flow is achieved, the access sheaths are flushed with heparinized saline, and angiography is performed to identify the culprit stenosis (Video 28.3). Balloon angioplasty (Video 28.4) is used to reduce the culprit stenosis (Video 28.5). Fogarty embolectomy extracts resistant thrombus at the arterial inflow (Video 28.6). The final step entails venography of the entire venous outflow and central veins to exclude the presence of a central venous stenosis (Video 28.7).

OUTCOMES

Success Rates

The acute success rate for endovascular treatment depends on access type and failure mode. Success, as defined by the ability to complete hemodialysis, ranges from 78% to 87% after catheter-based treatment of thrombosed AVFs and from 93% to 96% after treatment of thrombosed AVGs.^{14,15,21} Six-month patency rates range from 61% to 66%, and 1-year patency rates range from 38% to 41%.^{14,15} AVFs have longer median patencies than do AVGs.^{14,15}

Complications

Complications from endovascular treatment of dialysis access failure are rare but usually mild and controllable. Hematomas are graded on a scale from mild to severe.¹¹ Grade I hematomas are minor and non-flow limiting. Grade II hematomas are large and flow limiting. Grade III

hematomas are massive, associated with pulsatile extravasation or free perforation. Grade IV hematomas are associated with free-flowing rupture, which usually requires firm external compression, upsizing to an 11-Fr sheath, and placement of a Viabahn Endoprosthesis (WL Gore and Associates), Fluency Plus Tracheobronchial Stent Graft (Bard Peripheral Vascular), polyethylene teryltolate-covered Wallgraft (Boston Scientific), or surgical correction. Pinhole perforations can be controlled by manual compression alone or by placement of a cutaneous suture.²²

NEWER APPROACHES

Several experimental methods are under investigation to enhance the long-term patency of AV access.

Stent Grafts

Stents are usually reserved for severe recoil, venous perforations, or recurrent stenoses, but the use of a Fluency Plus Endovascular Stent²³ or a Viabahn Endoprosthesis^{24,25} may reduce restenosis compared with balloon angioplasty alone.

Interventional Nephrology

Most hemodialysis access interventions are performed in outpatient laboratories by interventional nephrologists during business hours, but some procedures require the urgent scheduling familiar to interventional cardiologists who treat patients with unstable angina or acute myocardial infarction.⁷ Many interventional cardiologists have more than 20 years of experience performing AV access procedures on demand 7 days a week and have maintained a successful collaboration with interventional nephrologists and clinical nephrologists who provide all the medical care for patients with ESKD.

Preemptive Angiography

Several studies have evaluated the ability of preemptive angioplasty to prevent access thrombosis. One study²⁷ evaluated the cost effectiveness of access blood-flow measurements and preemptive angioplasty in 159 patients and observed that a threefold increase in the number of angiographic procedures offset a 77% reduction in thrombosis events and a 65% reduction in fistula loss, thus defining an “economically dominant therapy” (i.e., cost saving). Another economic analysis²⁸ suggested that preemptive percutaneous transluminal angioplasty reduced the thrombosis rate from 28 to 22 per 100 patient-years ($P < .029$) at a net cost of \$34,586 per 100 patient-years and an incremental cost-effectiveness ratio of \$6177 per thrombosis event avoided.

Salvage of Hypoplastic Fistulas

In newly created AVFs that fail to undergo hypertrophy, balloon angioplasty of a stenosis at the arterial-venous

anastomosis can allow a hypoplastic fistula to undergo adaptive remodeling and become suitable for use.¹²

In some circumstances, surgical approaches are required. Surgical ligation of tributaries, superficialization of deep fistulas, or revision of anastomoses can salvage a significant number of hypoplastic fistulas that fail to mature adequately. When fistulas or grafts need repeated balloon angioplasty to treat restenosis, surgical excision with end-to-end repair may be needed.

SUMMARY

The life expectancy for patients on hemodialysis is directly related to hemodialysis access patency. When there is close collaboration between interventional cardiologists and nephrologists, patients with malfunctioning accesses can undergo prompt catheter-based treatments and avoid temporary catheters or an interruption in hemodialysis. Additional studies are required to identify treatments that reduce stenosis formation in hemodialysis AVFs and AVGs to improve overall survival and quality of life for patients with ESKD.

REFERENCES

1. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2019;73(3 suppl 1):A7-A8.
2. Saran R, Li Y, Robinson B, et al. US Renal Data System 2015 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2016;67(3 suppl 1):Svii, S1-S305.
3. US Renal Data System. *USRDS 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States.* Bethesda, MD: National Institute of Health, National Institutes of Diabetes and Digestive and Kidney Diseases; 2003.
4. Weiswasser JM, Sidawy AN. Strategies of arteriovenous dialysis access. In: Rutherford RB, ed. *Vascular Surgery.* Elsevier Saunders; 2005:1669-1676.
5. Vascular Access 2006 Work Group. NKF-DOQI clinical practice guidelines for vascular access, update 2006. *Am J Kidney Dis.* 2006;48(suppl 1):S176-S306.
6. Lok CE, Huber TS, Lee T, et al. KDOQI Vascular Access Guideline Work Group. KDOQI clinical practice guideline for vascular access: 2019 update. *Am J Kidney Dis.* 2020;75:S1-S164.
7. Bittl JA. Dialysis access intervention: techniques for the interventional cardiologist. *Prog Cardiovasc Dis.* 2021;65:84-88.
8. Dember LM, Beck GJ, Allon M, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. *JAMA.* 2008;299:2164-2171.
9. Dixon BS, Beck GJ, Vazquez MA, et al. Effect of dipyridamole plus aspirin on hemodialysis graft patency. *N Engl J Med.* 2009;360:2191-2201.
10. Perera GB, Mueller MP, Kubaska SM, Wilson SE, Lawrence PF, Fujitani RM. Superiority of autogenous arteriovenous hemodialysis access: maintenance of function with fewer secondary interventions. *Ann Vasc Surg.* 2004;18:66-73.
11. Beathard GA. Management of complications of endovascular dialysis access procedures. *Semin Dial.* 2003;16(4):309-313.
12. Bittl JA, von Mering GO, Feldman RL. Adaptive remodeling of hypoplastic hemodialysis fistulas salvaged with angioplasty. *Catheter Cardiovasc Interv.* 2009;73(7):974-978.
13. Roy-Chaudhury P, Arend L, Zhang J, et al. Neointimal hyperplasia in early arteriovenous fistula failure. *Am J Kidney Dis.* 2007;50:782-790.
14. Beathard GA, Lok CE, Glickman MH, et al. Definitions and end points for interventional studies for arteriovenous dialysis access. *Clin J Am Soc Nephrol.* 2018;13(3):501-512.
15. Bittl JA, Feldman RL. Prospective assessment of hemodialysis access patency after percutaneous intervention: Cox proportional hazards analysis. *Catheter Cardiovasc Interv.* 2005;66(3):309-315.
16. Sise ME, Baggett MV, Shepard JO, Stevens JS, Rhee EP. Case 17-2020: a 68-year-old man with Covid-19 and acute kidney injury. *N Engl J Med.* 2020;382(22):2147-2156.
17. Ascher E, Hingorani A. The Dialysis Outcome and Quality Initiative (DOQI) recommendations. *Semin Vasc Surg.* 2004;17(1):3-9.
18. Bittl JA. A proposal to reduce contrast nephropathy: eliminate the NPO order. *Catheter Cardiovasc Interv.* 2014;83(6):913-914.
19. Maleux G, Vander Mijnsbrugge W, Henroteaux D, et al. Multicenter, randomized trial of conventional balloon angioplasty versus paclitaxel-coated balloon angioplasty for the treatment of dysfunctioning autologous dialysis fistulae. *J Vasc Interv Radiol.* 2018;29(4):470-475.e3.
20. Lookstein RA, Haruguchi H, Ouriel K, et al. Drug-coated balloons for dysfunctional dialysis arteriovenous fistulas. *N Engl J Med.* 2020;383(8):733-742.



21. Bittl JA. Catheter interventions for hemodialysis fistulas and grafts. *JACC Cardiovasc Interv.* 2010;3:1-11.
22. Bittl JA. Venous rupture during percutaneous treatment of hemodialysis fistulas and grafts. *Catheter Cardiovasc Interv.* 2009;74(7):1097-1101.
23. Haskal ZJ, Trerotola S, Dolmatch B, et al. Stent graft versus balloon angioplasty for failing dialysis-access grafts. *N Engl J Med.* 2010;362(6):494-503.
24. Vesely T, DaVanzo W, Behrend T, Dwyer A, Aruny J. Balloon angioplasty versus Viabahn stent graft for treatment of failing or thrombosed prosthetic hemodialysis grafts. *J Vasc Surg.* 2016;64(5):1400-1410.e1.
25. Haskal ZJ, Saad TF, Hoggard JG, et al. Prospective, randomized, concurrently-controlled study of a stent graft versus balloon angioplasty for treatment of arteriovenous access graft stenosis: 2-year results of the RENOVA study. *J Vasc Interv Radiol.* 2016;27(8):1105-1114.e3.
26. Levit RD, Cohen RM, Kwak A, et al. Asymptomatic central venous stenosis in hemodialysis patients. *Radiology.* 2006;238(3):1051-1056.
27. Tessitore N, Bedogna V, Poli A, et al. Adding access blood flow surveillance to clinical monitoring reduces thrombosis rates and costs, and improves fistula patency in the short term: a controlled cohort study. *Nephrol Dial Transplant.* 2008;23:3578-3584.
28. Bittl JA, Cohen DJ, Seek MM, Feldman RL. Economic analysis of angiography and preemptive angioplasty to prevent hemodialysis-access thrombosis. *Cathet Cardiovasc Interv.* 2010;75:14-21.



29

Aortic Valvuloplasty And Transcatheter Aortic Valve Replacement

SUSHEEL K. KODALI, VIVIAN G. NG AND, MARTIN B. LEON

INTRODUCTION, 521

BALLOON AORTIC VALVULOPLASTY, 521

Procedural Considerations, 521

Outcomes, 522

Indications, 522

Next-Generation Balloon Aortic Valvuloplasty Devices, 522

TRANSCATHETER AORTIC VALVE REPLACEMENT (IMPLANTATION):

GENERAL CONCEPTS, 523

Historical Perspectives and Unmet Clinical Need, 523

Clinical Indications, 523

Heart Team Model and Risk Assessment, 524

Anatomic Screening and Need for Multimodality Imaging, 524

Procedural Considerations, 524

BALLOON-EXPANDABLE VALVES, 525

Technology Overview and Early Access Approaches, 525

Procedural Details for SAPIEN 3

Ultra Implantation, 526

Alternative Access Approaches, 527

Early Feasibility Trials, 527

SOURCE and Other Registries, 527

The PARTNER Trial, 530

The PARTNER II Trial, 536

The PARTNER III Trial, 537

SELF-EXPANDING VALVES, 537

Technology Overview, 537

Procedural Details for CoreValve

Implantation, 538

Alternative Access Approaches, 539

Overview of Registry Data and ADVANCE, 539

CoreValve US Pivotal Trial, 540

SURTAVI Trial, 540

Evolut Low Risk Trial, 541

“REAL-WORLD” REGISTRIES, 542

NEW CLINICAL INDICATIONS, 542

Bioprosthetic Valve Failure, 542

Transcatheter Aortic Valve Replacement for

Bicuspid Aortic Valve, 543

Transcatheter Aortic Valve Replacement for

Native Aortic Valve Regurgitation, 543

COMPLICATIONS OF TRANSCATHETER AORTIC VALVE REPLACEMENT, 544

Stroke, 544

Paravalvular Regurgitation, 544

Conduction Abnormalities and Arrhythmias, 545

Vascular Complications and Bleeding, 546

Other Less Frequent Complications, 546

NEW TRANSCATHETER AORTIC VALVE REPLACEMENT DEVICES, 547

Overview, 547

Self-Expanding Transcatheter Aortic Valve Replacement Systems, 547

Other Transcatheter Aortic Valve Replacement Concepts, 548

FUTURE DIRECTIONS, 548

CONCLUSIONS, 549

INTRODUCTION

Balloon aortic valvuloplasty (BAV) was developed as one of the first minimally invasive approaches to treat patients with symptomatic severe aortic stenosis (AS). Alain Cribier first described the procedure in 1986 in a case series of three patients with severe calcific AS.¹ Although the procedure was initially intended to be a minimally invasive alternative to surgical aortic valve replacement (SAVR), recognition of a high procedural complication rate, early restenosis, and lack of a mortality benefit eventually limited its overall utility.

Transcatheter aortic valve replacement (TAVR) or implantation (TAVI) has become a viable and durable therapy for patients with severe AS. Since Alain Cribier first described the TAVR procedure in 2002,² it is estimated that more than 450,000 procedures have been successfully performed worldwide in more than 750 centers. During the past 2 decades, procedural success, patient safety, and valve performance have improved dramatically because of technology enhancements, technique refinements, better patient selection, and a greater understanding of early and late clinical outcomes.

This chapter reviews the following: techniques for BAV, outcomes and complications with BAV, current indications

for BAV, newer BAV technology, historical perspectives of TAVR, techniques for implantation of transcatheter valves, current and expanded clinical TAVR indications, updated TAVR clinical trial results, complications of TAVR, and an overview of the next generation of TAVR devices.

BALLOON AORTIC VALVULOPLASTY

Procedural Considerations

Balloon aortic valvuloplasty is a procedure in which one or more balloons are placed across a stenotic valve and inflated to fracture the calcified aortic valve leaflets. The procedure results in separation of the commissures and stretching of the aortic valve annulus. The immediate hemodynamic results include an increase in aortic valve area (although rarely $>1.0 \text{ cm}^2$) and a reduction of the transvalvular gradient. Despite only modest changes in the valve parameters, the procedure can lead to meaningful, albeit short-term, symptomatic improvement in patients.

The BAV procedure can be performed via a retrograde or an antegrade approach. The retrograde approach is more commonly used and involves access via the femoral artery with a 10- to 14-Fr sheath. Anticoagulation is typically achieved with heparin dosing to achieve an activated

clotting time longer than 250 seconds, but bivalirudin can be used in patients with heparin allergy. An extra-stiff guidewire (0.035 inch) is used for the procedure and is required for stabilization of the balloon during inflation and deflation. Care must be taken to position the wire with a gentle curve in the left ventricular (LV) apex to avoid the risk of ventricular perforation. Typically, a slightly undersized balloon, about 1 mm smaller than the annulus, is used to minimize risk of annular rupture while maximizing results. If an adequate result is not obtained with initial inflation, a larger balloon sized to the annulus may be used. The various balloons available (Zymed, Tyshack, Cristal, True) have different profiles and compliance curves and are typically inflated manually. Rapid ventricular pacing (160–180 beats/min) via a temporary transvenous pacemaker or via the LV wire can be used to stabilize the balloon during inflation by reducing forward cardiac output. Care must be taken to avoid prolonged pacing runs, which may cause ischemia and hemodynamic compromise. Vascular closure can be achieved by manual compression or the “preclose” technique with either a 10-Fr Prostar or two Perclose ProGlide devices (Abbott Vascular).

The antegrade transvenous approach has also been used for BAV and requires creation of a transcirculatory loop from the femoral vein to the ascending aorta via a transseptal puncture. An Inoue balloon (Toray) or a traditional valvuloplasty balloon can be used. The potential benefits of the antegrade approach are reduced vascular complications, reduction of stroke, and greater increase in post-BAV area.³ However, it is more technically demanding given the need for a transseptal puncture and the subsequent looping of the guidewire in the LV apex.

Outcomes

The two largest registries that have evaluated BAV are the National Heart, Lung, and Blood Institute and the Mansfield Scientific registries. Both registries demonstrated high complication rates (20%–25%) and significant mortality rates during the hospitalization (8%).^{4,6} The most common complication was the need for a transfusion in 20% because of vascular access issues.

Although improved patient selection and technical improvements have led to a modest decrease in complication rates over the past 20 years, postprocedural morbidity remains high.^{7,8} In a more contemporary series of 262 high-risk surgical or inoperable patients with AS,⁷ the most common complications after BAV were intraprocedural death (1.6%); stroke (1.99%); coronary occlusion (0.66%); severe aortic regurgitation (AR; 1.3%); need for permanent pacemaker (0.99%); severe vascular complication (6.9%)—perforation (1.6%), ischemic leg (2.6%), pseudoaneurysm (1.99%), and arteriovenous fistula (0.66%); acute kidney injury (AKI; 11.3%); and new hemodialysis (0.99%). At approximately 6 months, there was a 50% mortality rate, and restenosis was evident as early as a few days after the procedure.

Given the frequency of these complications, their prompt identification and management are imperative. Despite smaller sheaths, vascular complications remain frequent, and operators must have the skill set to manage them using endovascular techniques with covered stents and prolonged

balloon inflations. The most devastating complication for patients remains cerebrovascular injury, which occurs in 1% to 2% of patients, as a result of atheroembolism from the ascending aorta or calcific embolism from the valve.^{7,8}

Indications

The 2020 American College of Cardiology/American Heart Association (ACC/AHA) guidelines⁹ on valvular heart disease specify that BAV might be reasonable (Class IIB recommendation) as a bridge to SAVR or TAVR in patients with severe AS. However, BAV is performed less frequently for this indication because TAVR outcomes have improved in high-risk patients.^{10–12} The updated 2020 European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) valve guidelines¹³ also give a Class IIB recommendation for BAV as a bridge to SAVR or TAVR in hemodynamically unstable patients who are at high risk for surgery or in patients with symptomatic AS who require urgent major noncardiac surgery. However, the ESC guidelines also state that BAV may be considered for palliation in patients unfit for SAVR or TAVR but do not designate a formal class recommendation.

Although BAV can be used as a bridge to TAVR in patients who are at extreme risk, it has also been used as a selection strategy for TAVR and SAVR in patients with severe AS but with other potential causes of their symptoms such as severe lung disease. Temporary improvement in symptoms after BAV support AS as the cause, and replacement of the aortic valve is warranted. And last, BAV has been used to temporize patients with acute hemodynamic failure while formulating a decision between SAVR, TAVR, and medical therapy.

Next-Generation Balloon Aortic Valvuloplasty Devices

With the advent of TAVR, there has been renewed interest in BAV. Several new devices have now been developed with the hope of improving both the safety and efficacy of BAV as a stand-alone procedure, as well as improving preparation (predilation) for subsequent TAVR. Four such devices are the InterValve V8 (InterValve), Bard TRUE dilation balloon catheter (Bard Medical), Atlas Gold dilation catheters (Bard Medical), True Flow balloon (Bard Medical), and the Pi-Cardia Leaflex system (Pi-Cardia).¹⁴ (Figure 29.1).

The InterValve V8 (see Figure 29.1A), Bard TRUE balloon (see Figure 29.1B), and Atlas Gold balloon (see Figure 29.1C) are approved by the US Food and Drug Administration (FDA) and available for use. Both of these devices attempt to address limitations of the current devices. The InterValve V8 has a dumbbell shape, which allows it to lock into the valve anatomy and limit balloon movement. The proximal bulb allows for hyperextension of the leaflets into the sinus to enhance valve opening, and the smaller waist reduces the risk of annular dissection. Furthermore, a rapid balloon inflation and deflation time minimizes ischemic time and hypotension. The Bard TRUE dilation balloon catheter is made of Kevlar composite balloon material with a precisely reproduced size and shape. It has also been designed for

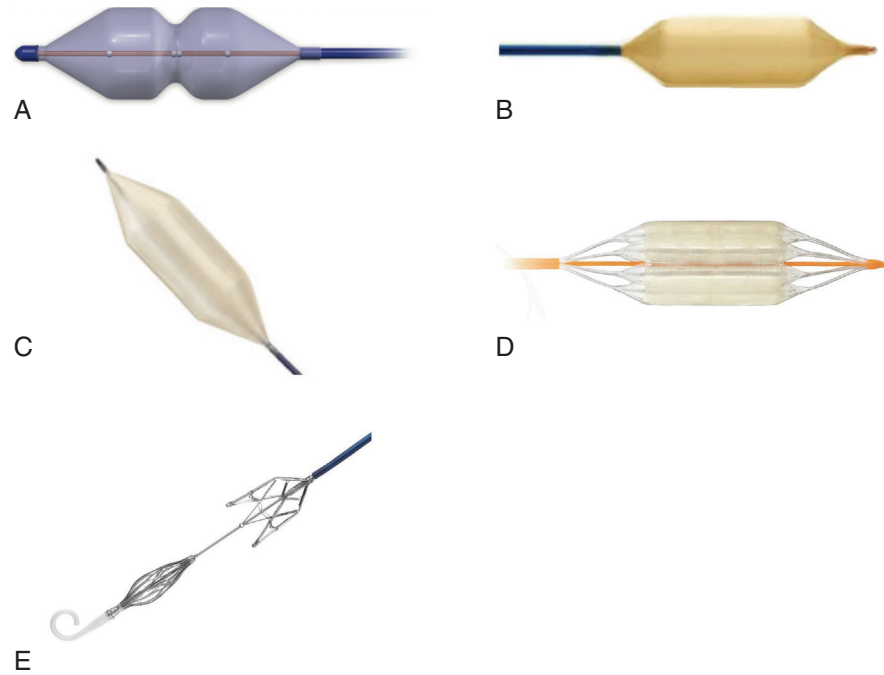


FIGURE 29.1 Next-generation valvuloplasty devices. **A**, V8 Aortic Valvuloplasty Balloon Catheter (InterValve). **B**, TRUE Dilatation Balloon Catheter (Bard). **C**, Atlas Gold (Bard). **D**, True Flow balloon (Bard). **E**, Leaflex Catheter System (Pi-Cardia). (**B**, © 2015 C. R. Bard, Inc. Used with permission. Bard and TRUE are trademarks and/or registered trademarks of C. R. Bard, Inc.).

fast inflation and deflation, rewinding, and puncture resistance. The Atlas Gold dilation catheter similarly is a non-compliant balloon but with less balloon growth.

The True Flow balloon (see Figure 29.1D) has a unique design and is composed of eight individual balloon chambers and a central open inner lumen. It was designed to allow continuous cardiac blood flow while the balloon is inflated through the open central lumen, thereby allowing reliable positioning without rapid ventricular pacing. This balloon was studied in the TRUE-FLOW (Evaluation of the BARD® True™ Flow Valvuloplasty Perfusion Catheter for Aortic Valve Dilatation) study, which was a single-center prospective trial of 24 patients.¹⁵ In this study 91.3% of patients underwent a successful BAV without clinically significant movement, and 91.7% of patients received no ventricular pacing. There were no device-related adverse events.

The Pi-Cardia Leaflex system (see Figure 29.1E) is currently undergoing investigation. The Pi-Cardia Leaflex system is not a balloon but a catheter that delivers mechanical shock waves to fracture calcium within the aortic valve. This allows for increased leaflet compliance with an increase in aortic valve area. Clinical results from both these devices may demonstrate their efficacy and potential role in patients.

TRANSCATHETER AORTIC VALVE REPLACEMENT (IMPLANTATION): GENERAL CONCEPTS

Historical Perspectives and Unmet Clinical Need

The first catheter-based aortic valve replacement was performed in 1965 by Davies¹⁶ in a canine model for the temporary relief of aortic insufficiency. Andersen et al.¹⁷ performed the first contemporary TAVR procedure using a

stent-based porcine bioprosthesis in pigs in 1992. The first implantation of a transcatheter valve in a human was performed by Bonhoeffer et al.¹⁸ in 2000 involving the percutaneous replacement of a pulmonary valve in a right ventricle to pulmonary artery prosthetic conduit using a bovine jugular valve to treat a 12-year-old boy with severe stenosis and regurgitation of the valved prosthesis. Cribier's first-in-human landmark TAVR procedure in 2002 was undertaken as a last resort in a patient with cardiogenic shock, failed BAV, and multiple comorbidities.² Since that time, TAVR has become the standard of care in patients who are "inoperable" and at high risk for conventional surgery.¹⁹ Although initial trials focused on high-risk and inoperable patients, additional randomized clinical trials have more recently evaluated TAVR in a broad spectrum of surgical risk patients.²⁰⁻²⁸ With improvements in TAVR technology and improved clinical outcomes, TAVR is now a widely accepted therapy for the treatment of patients with AS in all risk categories.

Clinical Indications

It is notable that in the past several years with improved TAVR clinical outcomes, there has been a general downshifting of the risk strata, such that traditionally lower-risk patients are being considered acceptable candidates for TAVR. In the current ESC/EACTS and ACC/AHA guidelines for the management of valvular heart disease,^{9,13} TAVR is the preferred therapy for patients with severe, symptomatic, calcific stenosis of a trileaflet aortic valve who

1. Have aortic and vascular anatomy suitable for TAVR, an expected survival longer than 12 months, and are high or prohibitive surgical risk assessment
2. Are symptomatic with severe AS and are older than 80 years of age or for younger patients with a life

expectancy less than 10 years and no anatomic contraindication to transfemoral TAVR

Acknowledging the benefits and risks of either SAVR or TAVR, currently guidelines recommend shared decision making with the patient when deciding between SAVR or TAVR in the following patient populations:

1. Symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindications to transfemoral TAVR
2. Asymptomatic patients with severe AS and an LVEF less than 50% who are 80 years of age or younger and have no anatomic contraindication to transfemoral TAVR

Heart Team Model and Risk Assessment

Given the complexity regarding the management of patients with severe AS, a collaborative heart team model is essential for appropriate patient selection and subsequent care.^{9,13} This multidisciplinary team consists of experienced cardiac surgeons, interventional cardiologists, imaging specialists, heart failure specialists, cardiac anesthesiologists, intensivists, neurologists, geriatricians, nurses, and social workers. The coordinated approach of the heart team results in more comprehensive patient evaluations, facilitated gathering of essential data, improved communication with patients and families, superior decision making, and ultimately, better clinical outcomes.

Several different surgical risk algorithms are used by heart teams for the selection of patients for TAVR. The two most common risk assessment tools are the Society of Thoracic Surgeons (STS) score and the logistic EuroSCORE.^{29,30} The two scores differ predominantly in the covariates used in the respective models and in the populations studied. Although both scoring systems aid in the selection of patients for TAVR, they serve as only one aspect of the selection process and should be used in the context of the entire clinical picture.

Several important concepts relevant to risk assessment for TAVR require further consideration, and many relevant risk factors are not represented in the standard risk scores, including frailty, dementia, hepatic disease, and anatomic factors (e.g., porcelain aorta or “hostile” chest). These ignored or underrepresented comorbidities must be considered by the heart team during risk assessment. At the extreme end of the risk spectrum are the so-called futile patients with AS, in whom there is little hope of meaningful quality of life or there is a limited life expectancy (e.g., untreatable malignancy or severe dementia) despite successful TAVR therapy. Although this may be a difficult societal conundrum, it is the responsibility of the heart team to thoughtfully identify these patients, such that TAVR may be sensitively withheld as a treatment option. Importantly, surgical risk is a continuum, and the categorization of risk status into discrete groups is somewhat arbitrary and depends on definitions that are changing over time and may be different in the rarified confines of a clinical trial versus real-world community standards. Finally, because the predictors of early and late outcomes after TAVR are different compared with SAVR, specific risk assessment models for TAVR would be clinically useful and are being actively evaluated.³¹

Anatomic Screening and Need for Multimodality Imaging

The information gathered during multimodality anatomic screening should be used to make an informed judgment on the candidacy of a patient for TAVR and in the overall management of patients with AS. The salient imaging data needed for comprehensive TAVR screening include (1) confirmation of the diagnosis of trileaflet, calcific, and severe valvular AS; (2) determination of LV size and function; (3) coronary artery anatomy; (4) peripheral vasculature of sufficient size and suitability for catheter access and prosthesis delivery; and (5) geometry, measurement, and calcium patterns of the left ventricular outflow tract (LVOT), proximal aorta, and the aortic annulus for appropriate device selection. Imaging for anatomic screening consists of a combination of echocardiography, angiography, and multislice computed tomography (MSCT).

Echocardiography is the gold standard for assessing the cause and severity of AS. Other important anatomic findings best determined by echocardiography are LV mass, size, and function; right ventricular (RV) size and function; and other valvular lesions (especially mitral and tricuspid regurgitation). Usually, transthoracic echocardiography (TTE) is sufficient, but in some patients with difficult imaging planes, transesophageal echocardiography (TEE) may be required. MSCT with contrast is the best imaging study to quantitatively measure the lumen dimensions of peripheral arteries and their suitability for a given TAVR system. MSCT is also the recommended imaging study to determine the optimal transcatheter valve size, which may differ depending on the specific transcatheter valve type. These three-dimensional (3D) reproducible measurements of the annulus region using validated algorithms derived from high-quality contrast MSCT have become the global standard modality in selecting the correct valve size. Intraprocedural 3D echocardiography can also be used to confirm the annulus measurements and to assist in valve sizing. Furthermore, MSCT is helpful in measuring the location and height of the coronary arteries; patterns of calcification in the aortic valve, aorta, and LV outflow tract; and the shape, angulation, and size of the proximal aorta. Assessment of coronary artery disease is necessary in patients before proceeding with TAVR. Assessment of the coronary tree for significant obstructive lesions can often be done with the aforementioned MSCT even though it is not a dedicated coronary CTA. Nonetheless, in some patients, coronary angiography may be necessary to determine the need for concomitant revascularization. This is especially true in younger and lower-risk patients in whom the presence of coronary disease may shift the balance in deciding between transcatheter and surgical therapy. Much of the success of TAVR and the recent improvements in clinical outcomes have been directly linked to meticulous preprocedural planning using the abovementioned multimodality imaging studies.

Procedural Considerations

Transcatheter aortic valve replacement is always performed in a sterile environment, either a catheterization

laboratory or an operating room, with angiographic digital imaging capabilities. In addition, many facilities have hybrid catheterization laboratory-operating room suites for TAVR. These hybrid procedure rooms combine the advantages of a high-resolution angiographic catheterization laboratory with the concomitant availability of a sterile environment for surgical management of complications and facilitate nonpercutaneous alternative access routes.

The presence of cardiac anesthesiology to supervise sedation and analgesia and to assist with hemodynamic monitoring and management has been an important requirement for TAVR to provide optimal care of these patients with high-risk AS. Although the more traditional approach incorporates general anesthesia with intraprocedural TEE to help guide the procedure (including confirmation of valve sizing and positioning, assessment of paravalvular regurgitation [PVR], and rapid recognition of complications), an increasing number of TAVR operators prefer a more “minimalist” approach, using only monitored anesthesia care (moderate sedation) instead of general anesthesia and employing only TTE, as needed.³² The reasons for this less-invasive TAVR strategy are reduced resource consumption, fewer anesthesia-related complications, more rapid patient ambulation, and shorter durations of hospital stay.^{33,34} Thus far, studies have demonstrated the feasibility of the minimalist approach, and experienced operators adopting this simplified approach have had equivalent procedural outcomes.^{35,36} A stratified patient-specific approach with shared patient decision making is most reasonable, wherein lower-risk patients or those with anticipated intubation morbidities (e.g., severe chronic obstructive pulmonary disease [COPD]) can be triaged to the minimalist strategy, and the higher-risk patients can be managed using a more intense strategy with general anesthesia and TEE guidance. As operator experience increases, likely the majority of TAVR worldwide will be performed in catheterization laboratories using conscious sedation.

BALLOON-EXPANDABLE VALVES

Technology Overview and Early Access Approaches

All TAVR systems are composed of three integrated components: a support frame (usually metallic), a bioprosthetic trileaflet valve, and a delivery catheter. The support frame is crimped onto the delivery catheter immediately before valve implantation and is expanded by either retracting a sheath or inflating an underlying balloon. Balloon-expandable TAVR systems (Edwards Lifesciences) were the earliest used in patients and have undergone several generations of evolution. However, many technology features have remained constant over time, including the tubular-slotted metallic frame geometry, pericardial bioprosthetic valve leaflets sewn to the frame, a fabric “skirt” covering the bottom of the frame, an out-of-body circumferential crimping of the valve, and frame assembly onto the delivery catheter. The Cribier-Edwards valve became available in 2004 and was used in many of the early feasibility cases in Europe and the United States. This TAVR system had both 23- and 26-mm valve sizes and a

stainless steel frame with an attached equine pericardial trileaflet valve that was directly crimped onto a commercial balloon valvuloplasty catheter. Cribier’s first case and many of the earliest cases were performed using an antegrade transfemoral vein approach, wherein after right femoral vein access, a transseptal puncture provided entry to the left heart followed by positioning a stiff guidewire across both the mitral and aortic valves. Navigating these first-generation devices and large-sized catheters with roughened distal edges across the interatrial septum and the tortuous intracardiac anatomy was challenging. The initial antegrade transfemoral vein transseptal access procedures required very experienced operators with advanced skills and resulted in many intraprocedural complications.³⁷ Specifically, the generation of a large guidewire loop inside the left ventricle, which was required to avoid traction on the anterior mitral valve leaflet, was extremely difficult to maintain throughout the procedure and often resulted in severe mitral regurgitation (MR) with hemodynamic collapse.

Difficulties with the unpredictability of the antegrade transseptal approach resulted in modifications of both the access approach and the delivery catheter. The femoral artery with retrograde transaortic entry into the left ventricle can be accomplished with direct percutaneous access or less commonly through an open surgical exposure of the common femoral artery. Webb and colleagues³⁸ reviewed their initial experience with the Cribier-Edwards valve via a retrograde transfemoral approach in a case series of 50 patients. For this purpose, a steerable delivery catheter with a deflectable tip was also developed to safely advance the TAVR system within the vasculature and to better align the valve assembly with the central valve orifice. In 2007, the next-generation Edwards SAPIEN (Edwards Lifesciences) transcatheter valve was introduced (Figure 29.2A). The major differences included a change from equine to bovine pericardium valve leaflet material, which enabled surgical valve-like consistency in tissue processing (decalcification, thickness, flexibility, and tensile strength), as well as further improvements in the delivery catheter. The third-generation SAPIEN XT valve (20-, 23-, 26-, and 29-mm sizes) began clinical evaluations in 2010 and represented a more radical design change of all system components, with a major goal to importantly reduce the overall profile (Figure 29.2B). The support frame had less metal and was changed from stainless steel to a thinner cobalt alloy; the valve geometry was modified to allow partial closing in the open position, and the delivery catheter was reduced in diameter by 33% for all valve sizes, with improved transitions to facilitate advancement and crossing. The marked reduction in system profile was in part due to an endovascular docking maneuver, such that the valve was crimped onto the catheter shaft for arterial entry, and in the descending aorta, the balloon was pulled back underneath the valve for subsequent deployment. The fourth-generation SAPIEN 3 device (Figure 29.3A) was evaluated in the PARTNER (Placement of AoRTic TraNscathetER Valve) II registry in the United States. The frame geometry was modified with larger cells distally, and in addition to the internal skirt, an external skirt was added to fill gaps and

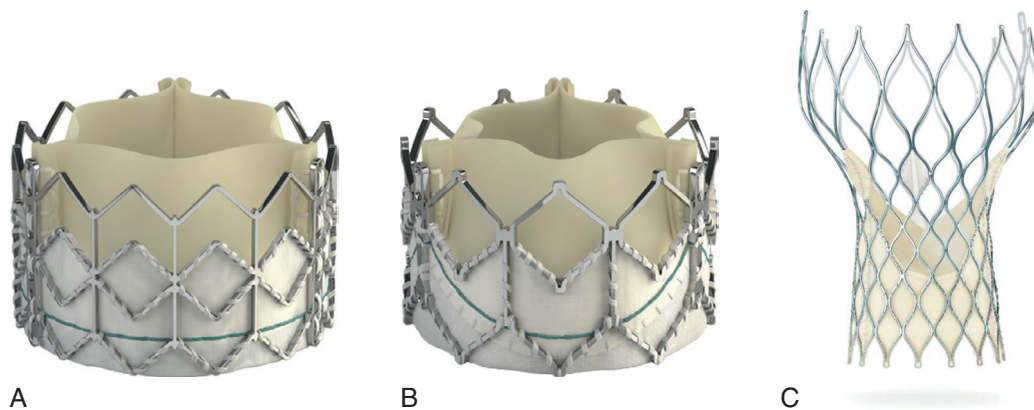


FIGURE 29.2 Prior generation of transcatheter valves. **A**, Edwards SAPIEN Valve (Edwards Lifesciences). **B**, SAPIEN XT (Edwards Lifesciences). **C**, CoreValve (Medtronic). (C, Copyright 2015, Medtronic, Inc.).

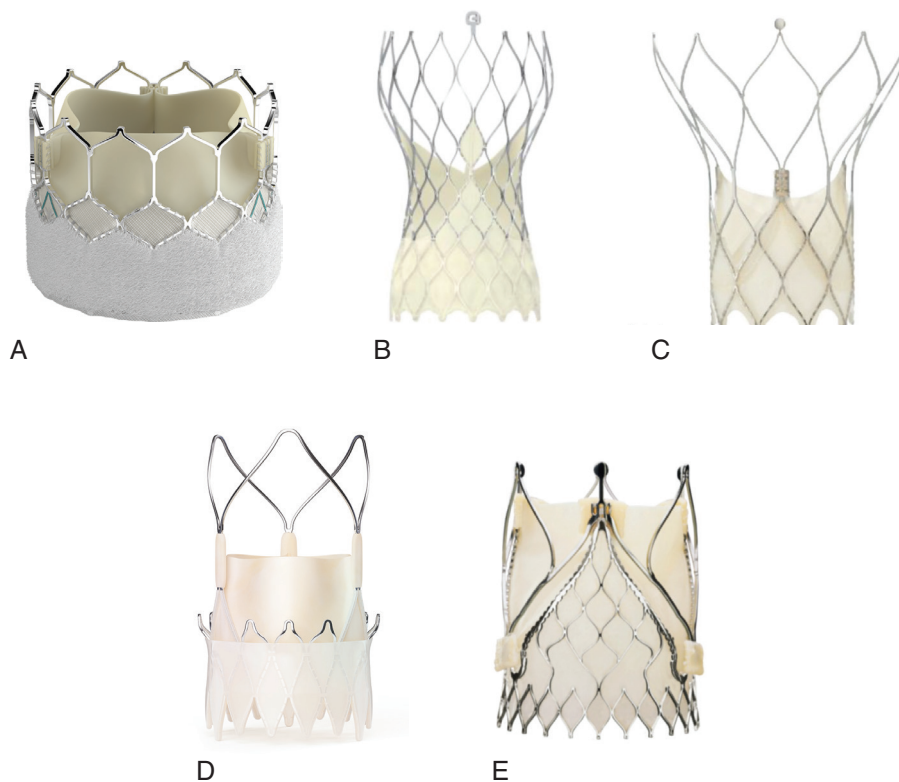


FIGURE 29.3 Current generation of transcatheter valves. **A**, SAPIEN 3 (Edwards Lifesciences). **B**, CoreValve Evolut R (Medtronic). **C**, Portico (St. Jude's Medical). **D**, Acurate (Image provided courtesy of Boston Scientific. © 2023 Boston Scientific Corporation or its affiliates. All rights reserved.). **E**, JenaValve (JenaValve). (B, Copyright 2015, Medtronic, Inc.)

to prevent PVR. The overall system profile was further reduced, with most valve sizes introduced through a 14-Fr expandable sheath. The latest generation SAPIEN 3 Ultra system builds on the SAPIEN 3 device by having a taller outer skirt composed of a textured polyethylene terephthalate structure to further reduce paravalvular leak. This device is Conformite Européenne (CE) marked and was approved by the FDA in 2018. A propensity-matched analysis of a registry of patients with AS who underwent TAVR with either the SAPIEN 3 or SAPIEN 3 Ultra valves found similar clinical outcomes (device success, major vascular complications, permanent pacemaker implantations, and moderate or greater PVR) between the two groups.³⁹ The SAPIEN 3 Ultra valve was initially designed to

be directly crimped onto the deployment balloon, which eliminated the need of docking the valve on the balloon and allowed a 14-Fr sheath to be used for all valve sizes. However, there were reports of balloon ruptures with the new delivery system during some valve implantations, and the FDA recalled the SAPIEN 3 Ultra delivery system.⁴⁰ As a result, the SAPIEN 3 Ultra is delivered via the prior generation SAPIEN 3 delivery system and sheath.

Procedural Details for SAPIEN 3 Ultra Implantation

The typical approach for balloon-expandable valve implantation is via the transfemoral approach. For the current

generation SAPIEN 3 Ultra, a 14-Fr e-sheath is required for the 20-, 23-, and 26-mm valves, and a 16-Fr e-sheath is required for the 29-mm valve. In addition to fluoroscopy, echocardiography (TTE or TEE) should be available for procedural guidance and postdeployment assessment. A temporary pacemaker is required for the procedure and is placed at the beginning via the femoral or internal jugular vein. Aortography is performed to identify a coplanar view for valve deployment. It is essential that the nadirs of all three cusps be in the same plane to ensure proper deployment of the valve (Video 29.1). The view can be identified by the preoperative computed tomography (CT) scan or through fluoroscopy and aortography.⁴¹ Arterial access for the valve delivery sheath can be obtained percutaneously and closure with the “preclose” technique.⁴² In the near future, there may be dedicated closure devices for large vessel access.

The remaining steps of the transfemoral retrograde TAVR procedure are as follows:

1. Placement of the valve delivery sheath
2. Guidewire crossing of the stenosed native aortic valve and positioning of a tightly curved Amplatz extra-stiff guidewire or a preshaped guide wire (Safari or Confida wires) in the LV apex
3. Although most operators avoid predilation, valvuloplasty can be performed with an undersized balloon using transient rapid RV pacing at heart rates of 180 beats to 200 beats/min to minimize pulsatile transaortic flow
4. Advancement of the steerable delivery catheter and crimped valve assembly through the vasculature to a coaxial position above the native valve
5. Crossing the native valve, retraction of the delivery sheath, and final positioning in a transvalvular location with approximately 60% to 70% of the prosthesis above the annulus confirmed using coplanar fluoroscopic views with or without echocardiography (prosthesis will shorten ~3 mm from the ventricular side during deployment) (Video 29.2)
6. Deployment of the bioprosthetic valve by slow balloon inflation during rapid RV pacing to ensure a stable platform (Video 29.3)
7. Assessment of PVR (by hemodynamics, angiography, and echocardiography)
8. If significant paravalvular AR is present, postdilation may be performed with addition of 1 to 2 cc of volume to the balloon delivery catheter (postdilation should not be performed in scenarios when there is increased risk for annular or root injury such as aggressive valve oversizing [$>20\%$] or severe LVOT calcification).
9. Removal of the catheters and suture-based closure of the percutaneous arteriotomy site or surgical repair of the access site

Alternative Access Approaches

In patients with severe peripheral artery disease or marked vessel tortuosity or with concerning pathological anatomy of the ascending aorta, there was a pressing need for an alternative to retrograde transfemoral arterial access. The first important nontransfemoral access site for balloon-expandable transcatheter valves was the antegrade transapical approach,⁴³ wherein the LV apex was exposed via a small

left anterolateral intercostal incision (fifth or sixth intercostal space) to expose the LV apex. After purse-string or mattress sutures are placed to secure the apex, direct needle puncture allows introduction of a hemostatic sheath into the left ventricle. The valve prosthesis is crimped in the antegrade direction onto the delivery catheter and is introduced through the sheath to an optimal transannular location followed by deployment with balloon expansion during rapid RV pacing. Bleeding from the apical entry site is always a concern, and careful surgical closure is required to avoid complications.

The transapical approach was often preferred by surgeon TAVR operators because it allowed for more precise control for valve positioning, less need for predilation, avoidance of “hostile” proximal aorta pathology, and an early perception of reduced periprocedural strokes. Disadvantages associated with the transapical approach include the possibility of early and late access site bleeding from the LV apex; hemodynamic instability caused by placement of a large intraventricular sheath, especially in patients with small hypercontractile ventricles or severe LV dysfunction; the requirement to use general anesthesia in all patients; and the sequelae of a left thoracotomy procedure, resulting in increased patient pain and delayed recovery. With the reduced catheter profiles of modern TAVR systems, the need for alternative transapical access has significantly diminished.

For these noted reasons, transapical access has dropped out of favor, and other alternative access concepts have been developed. Perhaps the most common alternative access approach is the subclavian or axillary artery approach via surgical cutdown with either direct access or use of a prosthetic graft to the artery or percutaneously.⁴⁴ The direct aortic approach is also used, because of the familiarity with standard surgical procedures involving exposure of the ascending aorta and aortic root cannulation. Other less commonly used access alternatives include direct iliac and distal descending aorta exposure via a retroperitoneal incision for placement of an iliac conduit, direct exposure of a carotid artery, and transcausal access with placement of a sheath from the inferior vena cava to the abdominal aorta followed by closure of the aortotomy hole using implantable occluder devices.

Early Feasibility Trials

After the initial first-in-human experiences with TAVR, four different nonrandomized feasibility studies for balloon-expandable Edwards transcatheter valves (Cribier-Edwards or Edwards SAPIEN) were conducted: Registry of EndoVascular Implantation of Valves in Europe II (REVIVE II), tRanscatheter EndoVascular Implantation of VALves II (REVIVAL II), Placement of AoRtic TraNscatheter VALves trial in Europe (PARTNER EU), and multicenter feasibility trial for TA-AVI (TRAVERCE).⁴⁵⁻⁴⁸ These feasibility registries demonstrated that TAVR could successfully be performed in a safe and efficacious manner in patients with high-risk AS and affirmed the short- to intermediate-term durability of the first-generation Edwards transcatheter valves.

SOURCE and Other Registries

The SOURCE (SAPIEN Aortic Bioprosthesis European Outcome) registry was created to gather clinical outcome

data on the Edwards SAPIEN 23- and 26-mm transcatheter valves for both the transfemoral and transapical approaches during the early phase of commercialization in Europe⁴⁹⁻⁵² (Table 29.1). At the time, it was the largest single registry of TAVR patients, and it was meant to reflect a consecutive case “real-world” experience. The Multicenter

Canadian Study is another real-world registry that captured the early experiences with balloon-expandable valves.^{53,54} These registries demonstrated that although the midterm mortality rate was high (~50%), most of the deaths were noncardiac and were likely related to the comorbidities of the patients. Importantly, the study

TABLE 29.1 Major Transcatheter Aortic Valve Replacement Registries for Patients with Severe Symptomatic Aortic Stenosis

REGISTRY	VALVE(S) USED	PATIENT POPULATION ^a	AVERAGE RISK SCORE ^b	ACCESS	MAJOR ENDPOINTS
SOURCE (cohorts 1 and 2)	ESV, 100%	<i>n</i> = 2307 Age, 81.6 y Women, 57.8%	EuroSCORE, 26.0%	TF, 60.2% TA, 39.8%	30 d: All-cause mortality, 9.6% Stroke, 4.7% Major vascular complication, 5% Major bleeding, 3.6% New PPM, 7% 1 y: TF: all-cause mortality, 7.5% Stroke, 2.9% New PPM, 6.7% TA: all-cause mortality, 10.9% Stroke, 2.5% New PPM, 7.1%
Canadian Multicenter	ESV/SXT, 100%	<i>n</i> = 339 Age, 81 y Women, 55.2%	STS, 9.8%	TF, 48.6% TA, 51.4%	30 d: Procedural success rate, 93.3% All-cause mortality, 10.4% (TF, 9.5%; TA, 11.3%) Stroke, 0.6% (TF, 0.6%; TA, 0.6%) Major vascular complication 13% (TF, 13%; TA, 13%) New PPM, 4.9% (TF, 3.6%; TA, 6.2%) 1 y: TF: all-cause mortality, 25%, TA: all-cause mortality, 22% 2 y: TF: all-cause mortality, 35%, TA: all-cause mortality, 36%
SOURCE XT	SXT, 100%	<i>n</i> = 2688 Age, 81.7 y Women, 57.3%	EuroSCORE, 20.5%	TF, 62.7% TA, 33.3% TAo, 3.7% TSc, 0.3%	30 d: All-cause mortality, 6.3% Stroke, 2.2% Major vascular complication, 14.5% Major bleeding, 8% New PPM, 9.5% 1 y: All-cause mortality, 19.5% Stroke, 6.3% All rehospitalizations, 29.4% Moderate or severe PVR, 6.2%
PREVAIL (TA and TF)	SXT, 100%	TA: <i>n</i> = 212 Age, 81.2 y Women, 29.2% TF: <i>n</i> = 141 Age, 83.7 y Women, 67.4%	TA: EuroSCORE, 24.1% TF: EuroSCORE, 22.4%	TF, 60% TA, 40%	TA 30 d: All-cause mortality, 7.5% Stroke, 1.5% Major vascular complications, 0.9% New PPM, 12% TA 1 y: All-cause mortality, 17% Stroke, 3.1% New PPM, 13.1% TF 30 d: All-cause mortality, 8.5% Stroke, 4.4% Major vascular complication, 11.4% New PPM, 8.7% TF 1 y: All-cause mortality, 17% Stroke, 6.8% New PPM, 13.5%
Piazza et al. ⁵⁵	MCV, 100%	<i>n</i> = 646 Age, 81 y Women, 54%	EuroSCORE, 23%	TF, 100%	30 d: Procedural success, 97% All-cause mortality, 8% Composite of death, stroke, or MI, 9.3%

TABLE 29.1 Major Transcatheter Aortic Valve Replacement Registries for Patients with Severe Symptomatic Aortic Stenosis—cont'd

REGISTRY	VALVE(S) USED	PATIENT POPULATION ^a	AVERAGE RISK SCORE ^b	ACCESS	MAJOR ENDPOINTS
Italian Registry	MCV, 100%	<i>n</i> = 659 Age, 81 y Women, 55.8%	EuroSCORE, 23%	TF, 90% TSc, 10%	30 d: All-cause mortality, 5.4% 1 y: Composite of death, major stroke, MI, and life-threatening bleeding, 30.4% All-cause mortality, 23.6% 2 y: Composite of death, major stroke, MI, and life-threatening bleeding, 36.5% All-cause mortality, 30.3% 3 y: Composite of death, major stroke, MI, and life-threatening bleeding, 40.3% All-cause mortality, 34.8%
Australia/ New Zealand Registry	MCV, 100%	<i>n</i> = 441 Age, 83.9 y Women, 44.9%	EuroSCORE, 17.3%	TF, 88.9% Other, 11.1%	1 y: MACCE, 22.1% All-cause mortality, 12% Stroke, 5.8% 2 y: MACCE, 32.9% All-cause mortality, 22.1% Stroke, 8.2%
ADVANCE	MCV, 100%	<i>n</i> = 1015 Age, 81.1 y Women, 50.5%	EuroSCORE, 19.4%	N/A	30 d: MACCE, 8% All-cause mortality, 4.5% Stroke, 3.0% 1 y: MACCE, 21.2% All-cause mortality, 17.9% Stroke, 4.5%
UK TAVI	ESV, 48%, MCV, 42%	<i>n</i> = 870 Age, 81.9 y Women, 47.6%	EuroSCORE, 19%	TF, 69% Other, 31%	30 d: Procedural success, 97% MACCE, 10.3% All-cause mortality, 7.1% Stroke, 4.1% Major vascular complication, 6.3% New PPM, 16% Moderate or severe AR, 14% 1 y: All-cause mortality, 21% 2 y: All-cause mortality, 26% Comparison of TF vs other access: TF had a lower mortality rate and surgical conversion but more AR and vascular complications ESV vs MCV: ESV had less AR, need for second valve, and PPM but greater surgical conversion
FRANCE 2	ESV, 67%, MCV, 33%	<i>n</i> = 3195 Age, 82.7 y Women, 49%	EuroSCORE, 22%	TA, 18% Non-TA, 82%	30 d: Procedural success, 96.9% All-cause mortality, 9.7% 1 y: All-cause mortality, 24% Stroke, 4.1% Incidence of all PVR, 64.5%

Continued

TABLE 29.1 Major Transcatheter Aortic Valve Replacement Registries for Patients with Severe Symptomatic Aortic Stenosis—cont’d

REGISTRY	VALVE(S) USED	PATIENT POPULATION ^a	AVERAGE RISK SCORE ^b	ACCESS	MAJOR ENDPOINTS
GARY	ESV, 53%, MCV, 42%, Other, 5%	<i>n</i> = 3875 Age, 82 y Women, 56%	EuroSCORE, 25%	TA, 30% Non-TA, 70%	TA 30 d: All-cause mortality, 9.0% TA 1 y: All-cause mortality, 28.0% Stroke, 3.6% New PPM, 14.1% Non-TA 30 d: All-cause mortality, 5.6% Non-TA 1 y: All-cause mortality, 20.7% Stroke, 4.8% New PPM, 26.2%
PRAGMATIC	ESV, 43%, MCV, 57%	<i>n</i> = 793 Age, 82 y Women, 47.2%	EuroSCORE, 21%	TF, 100%	MCV vs ESV at 30 days: Procedural success, 94% vs 96% All-cause mortality, 7.5% vs 5.0% Major stroke, 3.5% vs 1.5% Major vascular complication, 9.1% vs 15% Life-threatening bleed, 12% vs 14% PPM, 23% vs 5.9% MCV vs ESV at 1 y: All-cause mortality, 17% vs 14%

^aFor patient population, the age listed is the approximate average age of the population studied in any particular trial.
^bFor European trials, the logistic EuroSCORE is given, whereas for North American trials, the Society of Thoracic Surgeons (STS) score is given.
 ADVANCE, CoreValve Advance International Post Market Study: Evaluation of the Medtronic CoreValve System in a “Real-World” Patient Population; AR, aortic regurgitation; ESV, Edwards SAPIEN valve; FRANCE, French Aortic National Corevalve and Edwards-2; GARY, German Aortic Valve Registry; MACCE, major adverse cardiac and cerebral event; MCV, Medtronic CoreValve; MI, myocardial infarction; N/A, not applicable; PPM, permanent pacemaker; PRAGMATIC, Pooled-Rotterdam-Milano-Toulouse In Collaboration; PREVAIL, Placement of Aortic Balloon Expandable Transcatheter Valves Trial; PVR, paravalvular regurgitation; SOURCE, SAPIEN Aortic Bioprosthesis European Outcome; SOURCE XT, SAPIEN Aortic Bioprosthesis European Outcome XT; SXT, SAPIEN XT; TA, transapical, TAO, transaortic; TF, transfemoral; TSC, transsubclavian; UK TAVI, UK-TAVI: “UK Transcatheter Aortic Valve Implantation.”

demonstrated that unlike with BAV, valve areas remained stable, and there were no late changes in PVR and no cases of structural valve failure observed during the extended follow-up period.

The lower profile SAPIEN XT TAVR system was studied in three registries—PREVAIL TA, PREVAIL TF, and Edwards SAPIEN™ Aortic Bioprosthesis Multi-Region Outcome Registry XT (SOURCE XT).⁵⁶⁻⁶⁰ The largest of these was the multicenter SOURCE XT registry, which enrolled 2688 patients between July 2010 and October 2011.^{57,60} Vascular access in the trial was not limited to transfemoral and transapical but also included a small number of direct aortic access cases (3.7%). Unlike the original SOURCE registry, SOURCE XT included standardized Valve Academic Research Consortium (VARC) endpoint definitions, core laboratories, and an independent clinical events committee.⁶¹ Compared with SOURCE, patients in the SOURCE XT registry had a lower logistic EuroSCORE (overall, 20.4%); a significant minority (28%) did not have general anesthesia during the procedure; and because of the smaller delivery systems, patients were more likely to be treated using the transfemoral access route (62.7%) in contrast to earlier studies in which the majority were treated via transapical.

The all-cause mortality rate was lower in SOURCE XT than in the previous SOURCE registries, and vascular complications were no longer associated with increased mortality rates because of improved management strategies and fewer major events. Periprocedural (within 48 hours) and 1-month strokes were 2.2% and 6.3%, respectively, and the need for periprocedural pacemakers was 5.7%. The frequency of moderate or severe PVR was only 6.2% at 1 year.

There was dramatic symptom improvement in survivors at 1 year. The 1-year mortality rate was almost double in the transapical versus the transfemoral patients (27.2% vs 15.0%), and multivariate analysis clearly indicated that transapical access was a strong predictor of 1-year mortality (hazard ratio [HR] 1.64; 95% confidence interval [CI], 1.28–2.09; *P* < .0001).

The PARTNER Trial

The PARTNER trial is the seminal trial that demonstrated the safety and efficacy of TAVR for high-risk and inoperable patients with AS and set the benchmark for all subsequent TAVR device approval trials⁶²⁻⁶⁸ (Figure 29.4A and Table 29.2). PARTNER was the first multicenter, randomized controlled trial (RCT) of TAVR compared with accepted standard therapies in carefully defined patient populations. The results of this trial ultimately led to the approval of the Edwards SAPIEN valve by the FDA and has informed the worldwide cardiology community of the benefits and concerns of TAVR as an important new therapy for patients with AS.

During the course of PARTNER development and enrollment, it became clear that robust standardized clinical trial processes were necessary to assess study outcomes in patients with AS. The VARC was convened in 2009, including representatives from surgical and cardiology societies in Europe and the United States, prominent Academic Research Organizations, the FDA, and several expert consultants.^{61,70} Standardized endpoint definitions for all important clinical outcomes were carefully developed and

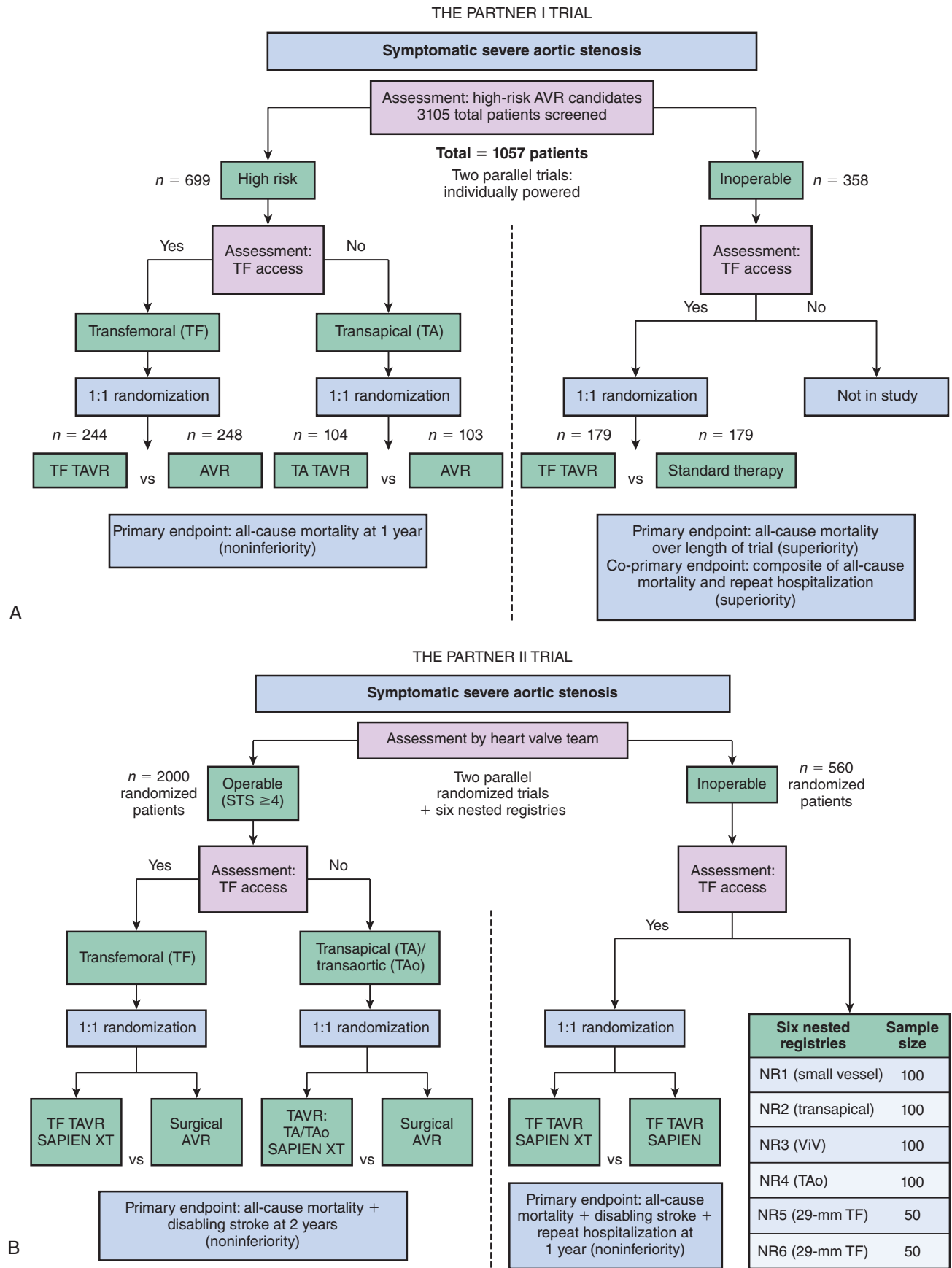


FIGURE 29.4 Study designs for randomized controlled transfemoral aortic valve replacement (TAVR) trials. **A**, The trial design of the PARTNER (Placement of Aortic Transcatheter Valve) trial with cohort A (high surgical risk) on the *left* and cohort B (inoperable) on the *right*. **B**, The trial design of the PARTNER II trial with cohort A (intermediate surgical risk) on the *left* and cohort B (inoperable) on the *right*, as well as the six nested registries (NRs).

Continued

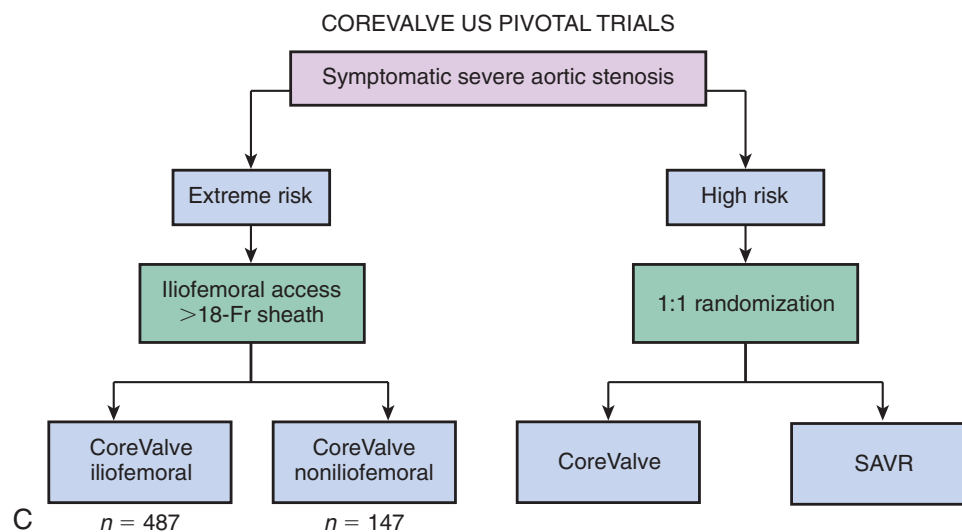


FIGURE 29.4, cont'd C, The trial design of the CoreValve US Pivotal Trial with the “extreme-risk” group on the *left* and “high-risk” group on the *right*. SAVR, Surgical aortic valve replacement; TA, transapical; ViV, valve-in-valve.

TABLE 29.2 Transcatheter Aortic Valve Replacement Randomized Controlled Trials for Patients with Severe Symptomatic Aortic Stenosis

TRIAL ¹²⁴	PRIMARY VALVE STUDIED	TREATMENT ARMS	POPULATION STUDIED	MAJOR STUDY RESULTS
PARTNER 1A 1-y outcomes	Edwards SAPIEN balloon-expandable valve	TAVR vs SAVR	High-risk surgical candidates (STS $\geq$ 0%) <i>n</i> = 699	30 d: All-cause mortality, 3.4% vs 6.5% (<i>P</i> = .07) Stroke, 4.6% vs 2.4% (<i>P</i> = .12) Major vascular complications, 11% vs 3.2% (<i>P</i> < .001) Major bleeding, 9.3% vs 19.5% (<i>P</i> < .001) Atrial fibrillation, 8.6% vs 16% (<i>P</i> = .006) 1 y: All-cause mortality, 23% vs 26.8% (<i>P</i> = NS) Stroke, 6.0% vs 3.2% (<i>P</i> < .08)
PARTNER 1A 2-y outcomes	Edwards SAPIEN balloon-expandable valve	TAVR vs SAVR	High-risk surgical candidates (STS $\geq$ 10%) <i>n</i> = 699	All-cause mortality, 33.9% vs 35% (<i>P</i> = NS) Stroke, 7.7% vs 4.9% (<i>P</i> = NS)
PARTNER 1A 3-y outcomes	Edwards SAPIEN balloon-expandable valve	TAVR vs SAVR	High-risk surgical candidates (STS $\geq$ 10%) <i>n</i> = 699	All-cause mortality, 44.2% vs 44.8% (<i>P</i> = NS) Stroke, 8.2% vs 9.3% (<i>P</i> = NS)
PARTNER 1B 1-y outcomes	Edwards SAPIEN balloon-expandable valve	TAVR vs standard therapy	Inoperable patients <i>n</i> = 358	30 d: All-cause mortality, 5.0% vs 2.9% (<i>P</i> = NS) Stroke, 5.0% vs 1.1% (<i>P</i> = .06) Vascular complications, 16% vs 1.1% (<i>P</i> < .001) 1 y: All-cause mortality, 31% vs 51% (<i>P</i> < .001) Death or hospitalization, 43% vs 72% (<i>P</i> < .001) NYHA Class $\geq$ III, 25% vs 58% (<i>P</i> < .001)
PARTNER 1B 2-y outcomes	Edwards SAPIEN balloon-expandable valve	TAVR vs standard therapy	Inoperable patients <i>n</i> = 358	All-cause mortality, 43% vs 68% (<i>P</i> < .001) Cardiac mortality, 31% vs 62% (<i>P</i> < .001) Stroke, 13.8% vs 5.5% (<i>P</i> = .01) Rehospitalization, 35% vs 73% (<i>P</i> < .001)
PARTNER 1B 3-y outcomes	Edwards SAPIEN balloon-expandable valve	TAVR vs standard therapy	Inoperable patients <i>n</i> = 358	All-cause mortality, 80.9% vs 54.1% (<i>P</i> < .001) Cardiac mortality, 74.5% vs 41.4% (<i>P</i> < .001) Rehospitalization, 75.5% vs 42.3% (<i>P</i> < .001)
PARTNER 2A	Edwards SAPIEN XT balloon-expandable valve	TAVR vs SAVR	Intermediate-risk surgical candidates (STS $\geq$ 4%) <i>n</i> = 2000	Enrollment completed; currently in the follow-up period

TABLE 29.2 Transcatheter Aortic Valve Replacement Randomized Controlled Trials for Patients with Severe Symptomatic Aortic Stenosis—cont'd

TRIAL ¹²⁴	PRIMARY VALVE STUDIED	TREATMENT ARMS	POPULATION STUDIED	MAJOR STUDY RESULTS
PARTNER 2B	Edwards SAPIEN XT balloon-expandable valve	TAVR with SAPIEN XT vs SAPIEN	Inoperable patients <i>n</i> = 358	30 d: All-cause mortality, disabling stroke, or rehospitalization, 17% vs 15.3% (<i>P</i> = NS) Major vascular events, 9.6% vs 15.5% (<i>P</i> = .04) Procedural: less anesthesia time, fewer aborted procedures, fewer multiple valve implants, and less need for hemodynamic support with SAPIEN XT 1 y: All-cause mortality, disabling stroke, or rehospitalization, 33.9% vs 34.7% (<i>P</i> = NS) All-cause mortality, 22.5% vs 23.7% (<i>P</i> = NS) Disabling stroke, 4.5% vs 4.6% (<i>P</i> = NS) Rehospitalization, 19% vs 17.4% (<i>P</i> = NS)
CoreValve Pivotal Trial Extreme Risk	Medtronic self-expanding CoreValve	Iliofemoral TAVR with CoreValve (standard therapy comparison arm removed after results of PARTNER 1B)	Inoperable patients <i>n</i> = 471	30 d: All-cause mortality or major stroke, 9.3% All-cause mortality, 7.9% Major stroke, 2.4% Moderate to severe PVR, 11.5% NPP, 22.2% 1 y: All-cause mortality or major stroke, 25.5% All-cause mortality, 24.0% Major stroke, 4.1% Moderate to severe PVR, 4.1% (no severe PVR) NPP, 27.1%
CoreValve Pivotal Trial High Risk	Medtronic self-expanding CoreValve	SAVR vs TAVR	High-risk surgical candidates (STS $\geq 10\%$) <i>n</i> = 699	30 d: All-cause mortality, 4.5% vs 3.3% (<i>P</i> = NS) MACCE, 10.4% vs 7.7% (<i>P</i> = NS) Major stroke, 3.1% vs 3.9% (<i>P</i> = NS) 1 y: All-cause mortality, 19.1% vs 14.2% (<i>P</i> = NS) MACCE, 27.3% vs 20.4% (<i>P</i> = .03) Major stroke, 7.0% vs 5.8% (<i>P</i> = NS)
SURTA VI	Medtronic self-expanding CoreValve	SAVR vs TAVR	Intermediate-risk surgical candidates (STS $\geq 4\%$ and $\leq 10\%$) <i>n</i> = 2000	Completing enrollment and entering follow-up period
CHOICE ⁶⁹	Edward SAPIEN XT/Medtronic self-expanding CoreValve	Balloon-expandable valves vs self-expanding valves	High-risk surgical candidates (STS $\geq 10\%$) <i>n</i> = 241	Procedural: All-cause mortality, 0% vs 0% (<i>P</i> = NS) Implant ≥ 2 valves, 0.8% vs 5.8% (<i>P</i> = .03) Device success, 95.8% vs 77.5% (<i>P</i> < .001) 30 d: All-cause mortality, 4.1% vs 5.1% (<i>P</i> = NS) Combined safety endpoint, 18.2% vs 23.1% (<i>P</i> = NS) Stroke, 5.8% vs 2.6% (<i>P</i> = NS) NPP, 17.3% vs 37.6% (<i>P</i> = .001)

CHOICE, A Randomized Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve Versus Edwards SAPIENXT; MACCE, major adverse cardiac and cerebral event; NPP, New permanent pacemaker; NS, not significant; NYHA, New York Heart Association; PARTNER, Placement of AoRTic Transcatheter Valve; PVR, paravalvular regurgitation; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons risk score; SURTA VI, Surgical Replacement and Transcatheter Aortic Valve Implantation; TAVR, transcatheter aortic valve replacement.

published in 2011. Thereafter, after testing these definitions in clinical trial settings, several additions and revisions were published as the VARC-2⁷⁰ consensus document in 2012 and subsequently the VARC-3⁷¹ consensus document in 2021. This dynamic process of creating optimal and standardized endpoint definitions has strengthened the TAVR evidence-based medicine effort.

The purpose of the PARTNER trial was to study the Edwards SAPIEN TAVR system in discrete high surgical risk patients. PARTNER began enrollment in 2007 and included 1057 patients with severe AS (defined as an aortic valve

area $< 0.8 \text{ cm}^2$ or aortic valve area index $< 0.5 \text{ cm}^2/\text{m}^2$ and a mean aortic valve gradient $> 40 \text{ mm Hg}$ or a peak aortic jet velocity $> 4.0 \text{ m/s}$), and cardiac symptoms (New York Heart Association [NYHA] Class II or greater) in two parallel randomized trials in whom conventional SAVR was associated with high or prohibitive risk. Patients were divided into two cohorts^{62,63}:

- Cohort A: those who were considered to be candidates for surgery despite being at high surgical risk, defined by an STS risk score of 10% or higher or the presence of coexisting conditions that would be associated with a

predicted risk of death by 30 days after surgery of 15% or higher

- Cohort B: those who were not considered to be suitable candidates for surgery because they had coexisting conditions that would be associated with a predicted probability of 50% or more of either death by 30 days after surgery or a serious irreversible condition

In the inoperable cohort, 358 patients were randomly assigned (1:1) to either transfemoral TAVR or to standard therapy (medical therapy with or without adjunctive BAV). In the high-risk cohort, 699 patients were randomly assigned (1:1) to either transfemoral TAVR or SAVR (244 vs 248 patients), or if the peripheral vascular anatomy was not suitable to accommodate the large sheaths, transapical TAVR or SAVR (104 vs 103 patients). The primary endpoint for both cohorts was all-cause mortality, with cohort

B powered for superiority versus standard therapy over the course of the trial and cohort A powered for noninferiority versus SAVR at 1 year. In both studies, the follow-up period was at least 1 year in all patients before assessing the primary endpoint results and other outcomes. Five-year follow-up findings have been reported from PARTNER in both the inoperable⁶⁸ and high-risk cohorts.⁷²

Patients in the inoperable cohort averaged 83 years old, more than half were female. Their mean STS score was 11.7%, multiple comorbidities were prevalent (including frailty and COPD), more than 90% had NYHA functional Class III or IV symptoms, and about 80% received BAV (at least once) in the standard therapy arm. The primary endpoint analysis at 1 year indicated a reduction in all-cause mortality rate from 50.8% with standard therapy to 30.7% after transfemoral TAVR ($P < .0001$; Figure 29.5A). The

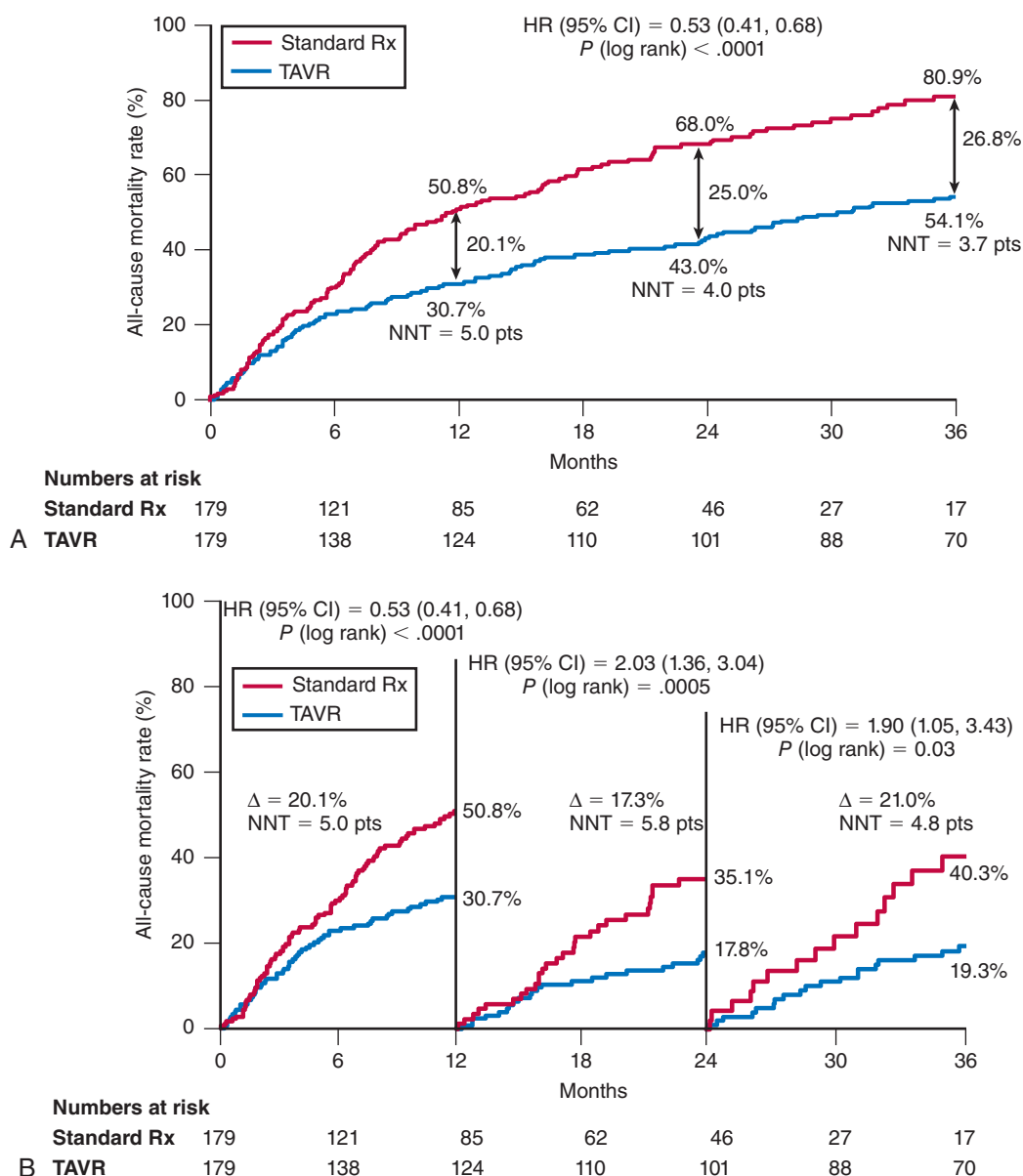


FIGURE 29.5 The 3-year outcomes of the PARTNER (Placement of Aortic Transcatheter Valve) trial. **A**, Cumulative hazard curves of all-cause mortality between patients randomized to transcatheter aortic valve replacement (TAVR) or standard therapy (cohort B). **B**, Landmark analysis for all-cause mortality for cohort B. The *left side* demonstrates the cumulative mortality rate in the two groups in the first year of follow-up. The *middle portion* shows the mortality rate in the second year of follow-up, conditional on survival up to 1 year. The *right side* shows the mortality rate in the third year of follow-up, conditional on survival up to 2 years.

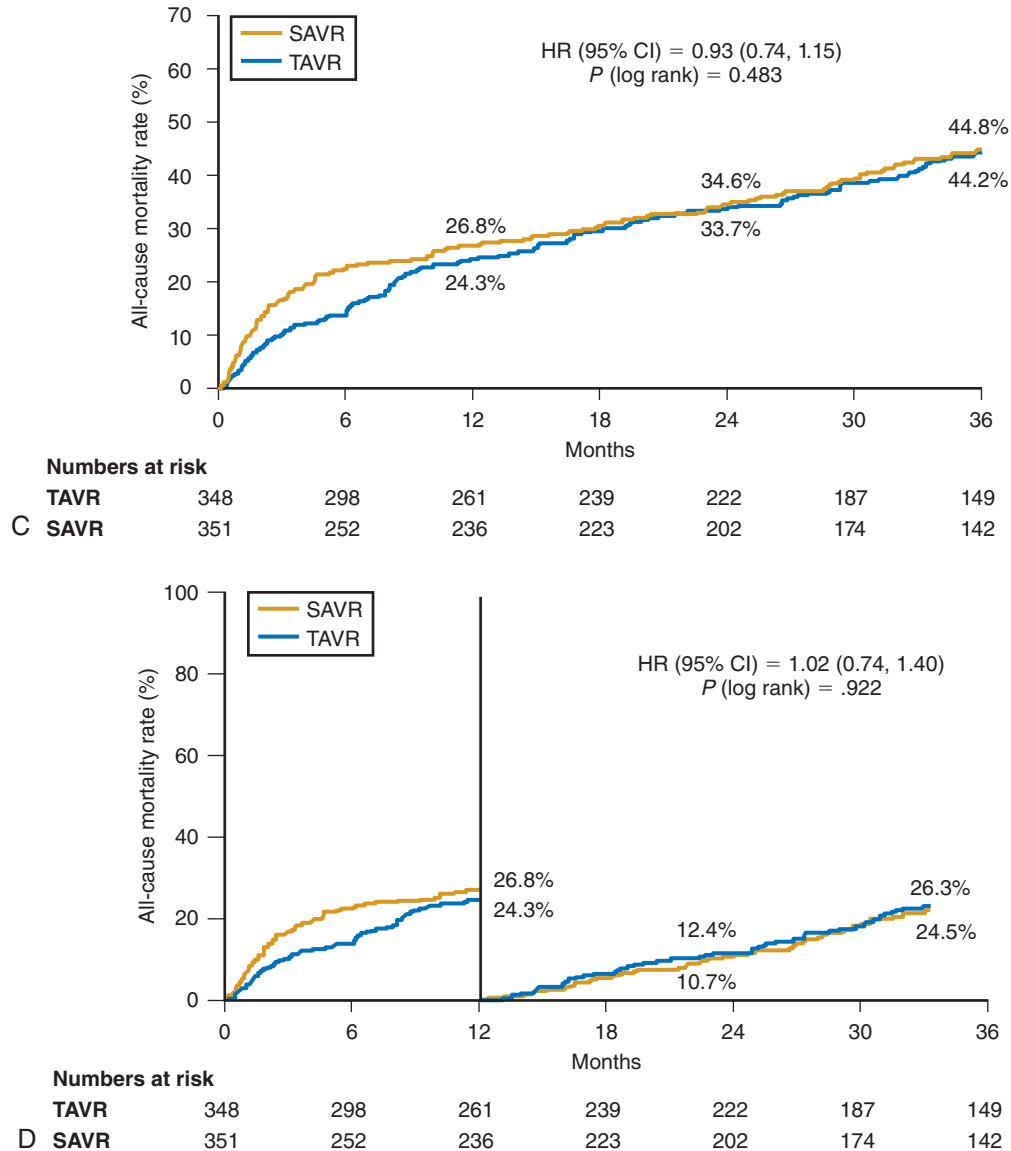


FIGURE 29.5, cont'd C, Cumulative hazard curves of all-cause mortality between patients randomized to TAVR and surgical aortic valve replacement (SAVR) (cohort A). **D**, Landmark analysis for all-cause mortality for cohort A. The *left side* demonstrates the cumulative mortality rate in the two groups in the first year of follow-up. The *right side* shows the mortality rate in the second and third years of follow-up, conditional on survival up to 1 year. CI, Confidence interval; HR, hazard ratio; NNT, number needed to treat; pts, patients; Rx, prescription.

number needed to treat was only five patients.⁶² This dramatic reduction in mortality was sustained over time with landmark analyses indicating incremental TAVR mortality benefits up to 3 years (Figure 29.5B).^{64,66,68} Importantly, in standard therapy patients who did not receive crossover to TAVR (allowed after 1 year) or out-of-protocol valve replacement, there was only one survivor at 5 years, which recapitulates the dire prognosis of “untreated” severe AS. Improved mortality rates after TAVR were demonstrated in all age groups, although they were limited in patients with the highest baseline STS scores (>15%).⁶⁸ Other benefits associated with TAVR therapy in these inoperable patients included significant reductions in rehospitalizations and improved cardiac symptoms with significant quality-of-life enhancement.^{62,64,66,68,73} Notable complications associated with TAVR therapy were major vascular complications and bleeding associated with the large delivery catheters, increased strokes (6.7% vs 1.7%) and PVR.

After the index hospitalization, there was no continuous hazard of increased strokes in the TAVR subgroup.^{66,68} Echocardiography core laboratory analyses showed after TAVR an improvement in LV function, regression of LV hypertrophy, a sustained increase in aortic valve areas with a decrease in transvalvular gradients, and no worsening of paravalvular AR. There were no signs of structural valve deterioration during the current 5 years of follow-up.

PARTNER patients in the high-risk cohort were also older (mean age, 84 years), the majority were male (57%), the mean STS score was 11.7%, and more than 90% had NYHA functional Class III or IV symptoms. There was a slight mortality benefit at 30 days with TAVR compared with SAVR (intention-to-treat analysis: 3.4% vs 6.5%; $P = .07$), but the primary 1-year mortality endpoint was similar in both groups (24.2% with TAVR vs 26.8% with SAVR; $P = .44$), and the noninferiority criteria were fulfilled (Figure 29.5C and D).⁶³ As demonstrated in previous studies, the mortality outcomes

at 30 days and 1 year were better in patients receiving transfemoral versus transapical TAVR. Follow-up to 5 years demonstrated continued similar mortality in the TAVR and SAVR cohorts.⁷² Although strokes at 30 days and 1 year were more frequent with TAVR (30 days, 4.6% vs 2.4%; $P = .12$; 1 year, 6.0% vs 3.2%; $P = .08$), stroke and transient ischemic events at 5 years were similar for both therapies (TAVR 14.7% vs SAVR 15.9%; $P = .61$). Other differences between TAVR and SAVR included increased vascular complications and PVR with TAVR and increased bleeding events with SAVR. The need for new permanent pacemakers at 1 month was similar with both therapies (TAVR 6.4%, SAVR 5.0%; $P = .44$). Transfemoral TAVR was also associated with reduced intensive care unit and hospital length of stay and earlier symptom benefit (by 30 days), although overall symptom improvement from baseline was equivalent and impressive with both therapies at 6 months and 1 year.⁷⁴ A cost-effectiveness analysis at 1 year indicated that transfemoral TAVR was cost-effective (reduced costs and improved quality adjusted life years) compared with SAVR in the PARTNER randomized high-risk cohort.⁷⁴ Echocardiography assessment of valve hemodynamics (gradients and areas) after valve replacement was similar for TAVR and SAVR, but there was significantly greater PVR in TAVR patients. During follow-up, even mild PVR after TAVR was associated with a significant increase in late death.^{65,72} However, there were no signs of structural valve deterioration at 5 years after either TAVR or SAVR.⁷²

Several already published substudies from the PARTNER trial are noteworthy. The high frequency of major vascular complications (~15%) in older adult patients (especially women) with frequent peripheral vascular disease, and their association with death has been highlighted⁷⁵ and stimulated efforts to reduce TAVR system profiles and develop more effective femoral access site closure techniques. Similarly, the importance of bleeding events (early and late), seen more commonly with SAVR than TAVR, was previously underappreciated and has been shown to have a significant impact on mortality.⁷⁶ A study of gender in PARTNER (high-risk cohort) demonstrated that women undergoing TAVR had lower 1-year and 2-year mortality rates compared with those undergoing SAVR ($P = .05$), which was amplified in the transfemoral patients ($P = .02$); there were no mortality differences in men.⁷⁷ Finally, in patients with preoperative moderate or severe MR, significant improvement in MR severity was shown at 30 days in the majority of patients after either treatment (69.4% after SAVR and 57.6% after TAVR),⁷⁸ but preoperative MR was a predictor of late death in only the SAVR cohort.

The PARTNER II Trial

The PARTNER II trial was a multicomponent study designed to evaluate the safety and efficacy of the lower profile SAPIEN XT TAVR system under a variety of conditions in comparison with the original SAPIEN valve. The first phase (PARTNER IIB; see Figure 29.4B) began enrollment in 2010 and was a prospective, multicenter trial in patients with severe inoperable AS. A total of 560 patients and were randomly assigned (1:1) to transfemoral TAVR

using either the original Edwards SAPIEN or the newer SAPIEN XT TAVR system. The primary endpoint was a non-hierarchical composite of all-cause mortality, disabling stroke, and repeat hospitalization at 1 year using a noninferiority study methodology. The 30-day mortality rate was low in both groups (Edwards SAPIEN, 5.1%; SAPIEN XT, 3.5%), and the composite outcomes were similar for both treatment cohorts at 1 year (Edwards SAPIEN, 34.7%; SAPIEN XT, 33.9%).⁷⁹ The main advantage of the SAPIEN XT system was the lower profile, which resulted in reduced (compared with Edwards SAPIEN) major vascular complications (from 15.5% to 9.6%; $P = .04$), disabling bleeding events (from 12.6% to 7.8%; $P = .06$), vascular perforations, and severe dissections.

The second phase of PARTNER II was a large multicenter randomized trial in patients with intermediate-risk AS, who were defined by an STS score of 4% or greater (or $\geq 3\%$ with documented comorbidities by the heart team) (PARTNER IIA; see Figure 29.4B). A total of 2032 intermediate-risk AS patients were randomly assigned (1:1) to either transfemoral SAPIEN XT TAVR versus SAVR, or if the peripheral vascular anatomy was not suitable to accommodate the catheters, either transapical or direct aortic SAPIEN XT TAVR versus SAVR. The primary endpoint was a composite of all-cause mortality and disabling stroke at 2 years, using a noninferiority study methodology. At 2 years, the rate was similar between TAVR and SAVR patients (19.3% vs 21.1%, respectively; HR, 0.89; 95% CI, 0.73–1.09; $P = .25$).²¹ There was no significant difference in outcome rates at 30 days and 1 year between TAVR and SAVR. For the first time, the rate of death of disabling stroke was lower in the subset of patients treated with transfemoral TAVR compared with those treated with SAVR (HR, 0.79; 95% CI, 0.62–1.00; $P = .05$). Although the 30-day rate of major vascular complications was higher in TAVR patients (7.9% vs 5.0%, $P = .008$), TAVR patients had lower rates of life-threatening bleeding (10.4% vs 43.4%, $P < .001$), AKI (1.3% vs 3.1%; $P = .006$), and new-onset atrial fibrillation (9.1% vs 26.4%; $P < .001$). Both TAVR and SAVR patients had a significant improvement in heart failure symptoms, aortic valve areas, and LV ejection fraction at 30 days. Paravalvular leak was seen at a higher frequency and severity in TAVR patients. TAVR patients with moderate or severe PVR had a higher mortality rate during 2-year follow-up than patients who had no or trace regurgitation ($P < .001$). At 5 years, there continued to be no significant difference in the primary composite endpoint between TAVR and SAVR patients (47.9% vs 43.4%; HR, 1.09; 95% CI, 0.95–1.25; $P = .21$).²⁴ However, there was a higher incidence of death from any cause with TAVR compared with SAVR in the 2- to 5-year landmark analysis. In addition, rates of aortic valve reinterventions were higher among TAVR patients (3.2% vs 0.8%). Nonetheless, these findings led to the expansion of guideline recommendations for TAVR for intermediate surgical risk patients with symptomatic severe AS.

In addition to the randomized trial, there were a series of nested registries in PARTNER II trial for the purpose of gathering data on various study topics, including the larger 29-mm valve size, the direct aortic access approach, and an aortic valve-in-valve registry for patients

with surgical bioprosthesis failure. Starting in 2013, the PARTNER II trial was expanded to include the newest SAPIEN 3 TAVR system in two large registries, including 550 patients who were either at high risk for surgery or were inoperable, and 1080 patients who were moderate risk for SAVR, including 76.3% of patients were included in the transfemoral access group and 23.7% of patients were included in the transthoracic access group.

Within the SAPIEN 3 registry, 1077 intermediate-risk patients received TAVR with the SAPIEN 3 valve. One-year outcomes in this population were compared with SAVR patients in the PARTNER 2A trial using a prespecified propensity score analysis, which contained 963 patients receiving the SAPIEN 3 valve and 747 patients who underwent SAVR.²² The rate of the primary composite endpoint (composite of mortality, strokes, and moderate or severe AR) was not only noninferior (pooled weighted proportion difference, -9.2%; CI, -12.4 to -6; $P < .0001$) but also superior (pooled weight proportion difference, -9.2%, 95% CI, -13.0 to -5.4; $P < .0001$) in the SAPIEN 3 TAVR population compared with the SAVR population. Therefore, the SAPIEN 3 valve is an improved iteration compared with the second-generation SAPIEN XT valve.

A prespecified analysis of the PARTNER II trial evaluating the incidence and impact of PVR on 1-year outcomes was conducted.⁸⁰ This multicenter nonrandomized registry contained 1592 patients at intermediate or high surgical risk TAVR who received the SAPIEN 3 valve. Within this registry, 55.7% of patients had nontrace PVR, 32.6% of patients had mild PVR, 8.2% of patient had mild to moderate PVR, and 3.5% had at least moderate PVR. Only patients with at least moderate PVR had higher 1-year rates of mortality (HR, 2.40; 95% CI, 1.3–4.43; $P = .005$) and mortality or rehospitalization (HR, 2.35; 95% CI, 1.52–3.62; $P < .001$) compared with other patients. Thus, this study demonstrated that although moderate or greater PVR was rare after SAPIEN 3 implantation, it was associated with increased risk of death and heart failure hospitalization at 1 year.

There has been increasing interest in the durability of TAVR valves because these valves are being used in lower-risk patient populations with longer life expectancies compared with high-risk and inoperable patients. To help address this question, the 5-year incidence of structural valve deterioration in intermediate-risk patients treated with either TAVR or SAVR in the PARTNER 2A trial and registry was evaluated.⁸¹ The SAPIEN -XT TAVR population had higher 5-year rates of structural valve deterioration ($1.61\% \pm 0.24\%$ vs $0.63\% \pm 0.16\%$), structural valve deterioration-related bioprosthetic valve failure ($0.58\% \pm 0.14\%$ vs $0.12\% \pm 0.07\%$), and all-cause (structural or nonstructural) bioprosthetic valve failure ($0.81\% \pm 0.16\%$ vs $0.27\% \pm 0.10\%$) compared with SAVR patients ($P < .01$ for all). In contrast, the SAPIEN 3 patients had similar rates of 5-year structural valve deterioration ($0.68\% \pm 0.15\%$ vs $0.60\% \pm 0.17\%$; $P = .71$), structural valve deterioration-related bioprosthetic valve failure ($0.29\% \pm 0.12\%$ vs $0.14\% \pm 0.08\%$; $P = .25$), and all-cause BVF ($0.60\% \pm 0.15\%$ vs $0.32\% \pm 0.11\%$; $P = .32$) compared with propensity score-matched SAVR patients. In addition, SAPIEN 3 patients had significantly lower 5-year rates of structural valve deterioration

and structural valve deterioration-related bioprosthetic valve failure compared with SAPIENT XT patients. Thus, these data also suggest that the SAPIEN 3 valve is a significant improvement over the SAPIEN XT valve. Additional studies are required to determine the long-term durability of balloon-expandable valves.

The PARTNER III Trial

The PARTNER III trial was a pivotal trial evaluating the safety and efficacy of TAVR for low-risk surgical AS patients.²⁶ In this multicenter trial containing 1000 patients, severe symptomatic AS patients determined to be at low surgical risk were randomized to either undergo transfemoral TAVR or to SAVR. The average STS risk score was 1.9%. The 1-year primary composite endpoint of death, stroke, or rehospitalization was significantly lower in TAVR patients compared with SAVR patients (8.5% vs 15.1%; 95% CI, -10.8 to -2.5; $p_{\text{noninferiority}} < .001$; HR, 0.54; 95% CI, 0.37–0.79; $p_{\text{superiority}} = 0.001$). TAVR was associated with lower 30-day rates of stroke (0.6% vs 2.4%; HR, 0.25; 95% CI, 0.07–0.88; $P = .02$). In addition, there were no significant difference in the rates of major vascular complications, new permanent pacemaker insertions, or moderate or severe PVR. At 2-year follow-up, the rate of the primary composite endpoint was still significantly lower in the TAVR group compared with the SAVR group (11.5% vs 7.4%; HR, 0.63; 95% CI, 0.45–0.88; $P = .007$).²⁸ Echocardiographic evaluation found that rates of hemodynamic valve deterioration and bioprosthetic valve failure were similar between TAVR and SAVR at 2 years. However, valve thrombosis was more frequently seen after TAVR than after SAVR. Thus, with improvements in TAVR technology resulting in improved outcomes with lower complication rates with TAVR therapies, the choice of whether to treat a patient with severe AS with either TAVR or SAVR requires individualized and nuanced patient-centered discussions by an experienced heart team. An important consideration in this patient population is valve durability because the life expectancy of this population will likely push the durability of these valves to their limits. Although initial data are encouraging, close follow-up of patients in these trials will be needed to determine the lifespan of these TAVR valves.

SELF-EXPANDING VALVES

Technology Overview

Self-expanding transcatheter valves offer an alternative to the balloon-expandable technology described earlier. The first of these is the CoreValve ReValving system (Medtronic), which was acquired by Medtronic in 2009. This design consists of a self-expanding nitinol frame that extends from the LVOT to the aortic root (see Figure 29.2C). The frame has three distinct zones:

1. An inflow portion with high radial forces to exclude the native valve and seal the annulus
2. A constrained portion designed to avoid the coronaries
3. An outflow portion that has low radial force to help orient the valve in the aorta

Within the constrained portion of the frame is a sewn porcine pericardial tissue valve, which is designed to be supraannular. This design allows the valve to remain circular at the coaptation point of the leaflets even in non-circular annular geometries, which, in theory, leads to optimized hemodynamics.

The first-generation device used bovine pericardial tissue and was delivered through a 24-Fr delivery system. The first human CoreValve implant was performed in July 2004 by Jean-Claude Laborde in India on a 62-year-old man with critical AS and multiple comorbidities.⁸² Although the implant was successful, the patient died 4 days later because of multiorgan failure. The second-generation device used porcine pericardial tissue, thereby reducing the crimped profile and allowing delivery through a 21-Fr sheath. A first-in-human trial with the first- and second-generation systems demonstrated acute device success of 88% but with an in-hospital mortality rate of 20%.⁸³ These initial procedures were performed with extracorporeal bypass for support and surgical cutdown for vascular access (common iliac, femoral, or subclavian). The third generation of the device reduced the profile further to 18 Fr, allowing for fully percutaneous delivery without hemodynamic support. Also, the frame design was modified to have a broader upper segment, allowing for improved fixation in the ascending aorta. A multicenter study of 86 patients using both the second- and third-generation devices demonstrated an acute device success rate of 88% with a procedural mortality rate of 6%.⁸⁴ In six patients, valve malpositioning led to urgent conversion to surgical valve replacement. The 30-day mortality rate was 12% with a combined mortality and major adverse cardiac events (MAACE) rate, including death, stroke, and MI, of 22%. Valve function and hemodynamics were excellent with significant reduction in mean gradients.

Based on these initial data, the Medtronic CoreValve received CE mark approval in 2007. In 2010, an updated delivery system incorporating the AccuTrak Stability Layer to minimize movement during deployment received CE mark. In January 2014, the device received FDA approval for inoperable patients, which was extended to include high-risk patients in June 2014 based on the results from the US Pivotal trial described later.

The next generation of CoreValve is the Evolut R with EnVeo R delivery system, which received CE mark approval in September 2014.⁸⁵ The valve had several refinements from the original CoreValve to improve anatomical fit, annular sealing, and durability. The nitinol frame had been designed to conform better to the annulus across different size ranges, which may reduce the stress on the conduction system and thereby reduce the frequency of permanent pacemakers. The height of the Evolut R frame had also been reduced so that it is approximately 10% shorter than the prior CoreValve. Plus, the pericardial skirt had been extended on the inflow side to improve annular seal and potentially reduce PVR. Finally, the delivery system (EnVeo Pro) was modified significantly to allow the valve to be recaptured and repositioned until final release. Moreover, the InLine sheath has been integrated into the delivery catheter so that the outer diameter of the entire system is 18 Fr, which is equivalent to a 14-Fr sheath.

The Evolut R valve was further modified to the Evolut Pro valve (see [Figure 29.3B](#)). The Evolut Pro valve includes an external tissue wrap, which increases the surface area contact between the valve frame and the native aortic annulus to decrease paravalvular leak. The Evolut Pro comes in 4 sizes (23, 26, 29, and 34 mm). This valve is currently delivered using the same 14-Fr EnVeo Pro system.

Procedural Details for CoreValve Implantation

The standard delivery route for CoreValve implantation is via the transfemoral approach, which requires two operators, and in general, the approach is similar across sites. Although general anesthesia is not required for the procedure, the use of TEE can be used to facilitate the assessment and management of PVR.⁸⁶ All patients have a temporary transvenous pacemaker placed at the beginning of the procedure. The vast majority of procedures are performed percutaneously using the “preclose” technique for vascular closure.⁴² The fluoroscopic view for valve deployment is identified by performing an aortogram with the pigtail catheter at the base of the noncoronary cusp ([Video 29.4](#)). More recently, a “cusp overlap” fluoroscopic projection has been recommended for self-expanding valve deployment.^{87,88} In this fluoroscopic projection, the right and left coronary cusps are overlapped while the noncoronary cusp is isolated. This is typically a right anterior oblique and caudal projection. The cusp overlap view aids in removing the parallax from the CoreValve frame and allows for a higher valve deployment to decrease the risk of permanent pacemaker implantation. The preoperative CT scan can be used to identify both the three-cusp and the cusp overlap coplanar views in advance.

The remainder of the procedure consists of the following steps:

1. A 14-Fr delivery sheath is placed from the femoral approach.
2. The aortic valve is crossed, and through a pigtail catheter, a stiff wire with a preshaped curve (e.g., Confida or Safari wire) is placed in the LV apex.
3. BAV with an undersized balloon can be performed at this point but is not necessary.⁸⁹
4. The CoreValve device is advanced across the aortic valve, and the fluoroscopic view is adjusted based on the distal marker of the sheath to ensure coaxial deployment of the valve.
5. The valve is positioned so that the first “node” is at the annulus, and the valve is slowly unsheathed by rotating the wheel on the delivery catheter.
6. Aortograms are performed as the valve flairs to ensure that device is landing about 3 mm below the annulus ([Video 29.5](#)).
7. Ventricular pacing at a rate of 100 to 120 beats/min can be performed at this point to stabilize the valve.
8. After the valve has made annular contact (one-third deployed), the valve can be unsheathed to the two-thirds position rapidly. (Blood pressure can drop at this point because of the prosthesis obstructing outflow.)
9. The valve is then released by completely unsheathing the prosthesis ([Video 29.6](#)).

10. Assessment of AR is performed by multiple modalities (hemodynamic assessment, aortography, echocardiography).^{90,91}
11. If significant PVR is present, postdilation can be performed with an appropriately sized balloon, which is typically the minimum diameter of the annulus as measured on 3D reconstructions. However, in the absence of high-risk features for annular rupture, such as severe LVOT calcification, a balloon sized to the mean diameter can be used.

Alternative Access Approaches

For patients without iliofemoral access, the CoreValve prosthesis can be placed via a subclavian or axillary or a direct aortic approach.^{92,93} The procedure for the subclavian or axillary approach involves obtaining access to the artery via surgical exposure or percutaneously. Use of the subclavian approach requires careful preoperative screening to ensure that the vessel size is adequate (minimal size, 5 mm) and that there is minimal tortuosity and calcification. In cases in which there is a patent left internal mammary artery supplying coronary flow, caution should be used, and the minimal vessel size at that level needs to be large enough to allow flow to the mammary even with the sheath in place.

When iliofemoral or subclavian access is not possible for CoreValve insertion, a direct aortic approach can be carried out. After gaining exposure to the ascending aorta, pledgeted purse-string sutures are placed. Operators must be careful to ensure that there is adequate distance (~7 cm) between the intended puncture site and the aortic valve. A 6-Fr sheath is then inserted within the purse-string sutures using a modified Seldinger technique. The aortic valve is then crossed in the standard fashion, and a pigtail catheter is advanced into the LV. A stiff wire with a pre-shaped curve is positioned in the LV apex, and the 6-Fr sheath is exchanged for the 14-Fr delivery sheath. Valve deployment then proceeds in the standard fashion without predilation of the valve. After deployment of the prosthesis, the purse-string sutures are tied under direct vision, and the chest wall is closed in regular surgical fashion.

Overview of Registry Data and ADVANCE

Several different registries have reported short-, intermediate-, and long-term outcomes with the third-generation CoreValve prosthesis.^{55,94–96} For example, Piazza et al.⁵⁵ first published a multicenter European registry of 646 patients to evaluate performance and outcomes after CE mark approval. These studies represent the early clinical experience with the CoreValve system. The procedural success rate in this early experience was 97% with a 30-day all-cause mortality rate of 8%.⁵⁵ These early registries demonstrated that implantation of a CoreValve prosthesis was feasible with high procedural success, and survival was reasonable with appropriate patient selection. In addition, although not adjudicated, these early studies identified important procedural complications.

The largest CoreValve registry to date is the ADVANCE (CoreValve Advance International Post Market Study: Evaluation of the Medtronic CoreValve System in a “Real-World”

Patient Population) study, which enrolled 1015 patients.⁹⁷ There were several unique aspects of this registry. First, all sites were experienced and had performed at least 40 procedures before participating. Second, all patients were monitored, and the primary endpoints were adjudicated by a clinical events committee. Finally, there was core laboratory assessment of echocardiograms and angiograms. Thirty-day MAACE, based on VARC criteria, was 8.0% with an all-cause mortality rate of 4.5%. The primary endpoint of 1-year MAACE (all-cause mortality, MI, emergent surgery or percutaneous reintervention, or stroke) was 21.2%. The 1-year all-cause mortality rate was 17.9%, and the stroke rate was 4.5%. Moderate or severe PVR was independently associated with a higher 1-year mortality rate (HR, 1.63). Requirements for new permanent pacemaker placement were 26.3% at 30 days and 29.2% at 1 year.

Conduction abnormalities are frequently noted after CoreValve implantation. The frequency of new bundle branch block (LBBB) has ranged from 35% to 57% in several studies with CoreValve,^{98–100} which is significantly higher than the rate seen after Edwards SAPIEN implantation.^{100–102} However, the impact of LBBB on clinical outcomes remains controversial. Although one study did demonstrate an increased mortality rate at 1 year in patients with a new left LBBB,¹⁰¹ subsequent studies have failed to corroborate this finding.^{99,102,103} Regardless, several reports have shown that patients with new LBBB show lack of improvement in LV function.¹⁰² Requirements for permanent pacemaker implantation in these early registries were significantly higher with CoreValve than with the SAPIEN transcatheter valves.¹⁰⁴ However, the presence of a new pacemaker does not appear to impact late mortality.^{105,106}

As noted earlier, the Medtronic self-expanding valve has iterated significantly to facilitate implantation and decrease complication rates. The Evolut R Clinical study studies the safety and efficacy of the next-generation device in a prospective, multicenter, nonrandomized single-arm study including 241 patients at high surgical risk.¹⁰⁷ Recapturing and repositioning the valve occurred in 22.6% of cases. At 30 days, rates of all-cause mortality (2.5%), disabling stroke (3.3%), major vascular complications (7.5%), life-threatening or disabling bleeding (7.1%), and permanent pacemaker implantation (16.4%) were similar to prior studies. Compared with prior trials, the rate of severe residual PVR appeared to be lower in this study (5.3%). Thus, it was concluded that this iterative improvement to the CoreValve self-expanding valve was safe and effective.

The valve further iterated to the currently used Evolut Pro valve which has an external skirt, which was compared in a propensity matched analysis containing 148 patients with high-risk AS who received the Evolut R valve and 74 patients receiving the Evolut Pro valve.¹⁰⁸ This study demonstrated no differences in hemodynamics between the two valves and similar rates of permanent pacemaker implantation (10.8% vs 18.6%; $P = .096$), disabling stroke (1.4% vs 0.7%; $P = 1.0$), major bleeding (1.4% vs 1.3%; $P = .87$), and vascular complications (0% vs 0%; $P = 1.0$). In addition, there was no difference in the rates of mild PVR between Evolut R and Evolut Pro patients (16.2% vs 14.9%; $P = .79$).

This study led to the Evolut PRO Clinical study, which was a prospective, multicenter, controlled, nonrandomized single-arm study that included 60 patients within the United States.¹⁰⁹ At 30 days, 1 (1.7%) patient had died, and 1 (1.7%) patient had a disabling stroke. The 30-day rate of major vascular complications was 10.0%, and 11.7% patients had a life-threatening or disabling bleed. This study demonstrated the benefit of the external wrap with no patients having moderate or severe PVR and 72.4% of patients having none or trace regurgitation. New permanent pacemaker implantations occurred in 10% of patients. Although this was a small study, these data were encouraging and suggested the safety of the Evolut Pro system in the treatment of patients with severe AS.

The Evolut Pro system was further evaluated in the FORWARD PRO Study Interventional Post-market Study With the Evolut™ PRO System (FORWARD PRO) prospective, multinational, multicenter, single-arm observational study.¹¹⁰ TAVR with the Evolut Pro valve was attempted in 629 patients between February 2018 and January 2019. The mean STS score of patients in this study was $4.7\% \pm 3.3\%$. The 30-day primary endpoint of all-cause mortality occurred in 3.2% of patients, which was lower than the prespecified performance goal (5.5%; $P = .004$). The VARC-2 composite safety endpoint (death, stroke, life-threatening bleeding, major vascular complication, stage 2 or 3 AKI, coronary artery obstruction requiring intervention or valve-related dysfunction requiring repeat aortic valve (AV) procedure) rate at 30 days was 9.4%. Even though the addition of the outer pericardial wrap on the Evolut Pro valve frame increased the device outer diameter by two French sizes, the rate of major vascular complications with this TAVR system remained low at 3.0% and was lower than prior reports with the Evolut R system. These studies suggest the safety and efficacy of the Evolut Pro valve.

CoreValve US Pivotal Trial

The CoreValve US Pivotal Study was designed to compare TAVR with standard therapies in patients with severe AS at either high or extreme risk for SAVR (see Figure 29.4C). Initially, the study was designed as two separate RCTs for both “high-risk” and “extreme-risk” groups as assessed by the heart team.^{111,112} However, after presentation of the PARTNER cohort B data showing survival benefit with TAVR over medical therapy, it was deemed unethical to randomize patients to medical therapy. Therefore, the study design was changed to a registry of about 500 extreme-risk patients undergoing iliofemoral TAVR with Core-Valve compared with an objective performance goal (OPG) derived from seven contemporary BAV studies as well as the medical arm of PARTNER cohort B. In addition, there was a simultaneous registry of 150 patients who underwent noniliofemoral TAVR. The “high-risk” group was defined by an operative mortality of 15% or greater, and the patients in that group were randomized to SAVR or CoreValve TAVR. The primary endpoint for the “extreme-risk” group was all-cause mortality and major stroke at 12 months; for the “high-risk” group, it was all-cause mortality at 12 months.

The Extreme Risk Study enrolled patients in the United States between February 2011 and August 2012.¹¹² The as-treated population consisted of 489 patients in whom

iliofemoral TAVR was attempted. The patient population was an older adult comorbid population similar to the cohort B population in the PARTNER trial. The valve was successfully implanted in 486 patients. The trial met its primary endpoint of all-cause mortality and major stroke at 1 year with a rate of 26.0%, which was significantly lower than the OPG of 43% (Figure 29.6A). At 1 month, the rate of stroke was 4.0%, and it remained low over time with a 1-year rate of 7.0%. Other important complications included major vascular (8.2%) and major or life-threatening bleeding (36.7%). Conduction abnormalities were frequent, and new permanent pacemakers were required in 21.6% of patients at 30 days. Valve hemodynamics were excellent with a reduction of mean gradient to 8.9 mm Hg with an effective orifice area of 1.9 cm² at 12 months. Moderate or severe AR was present in 13.8% of patients at discharge. Only severe AR was associated with an increased 1-year mortality rate. Interestingly, PVR appeared to decrease over time with 82.8% of patients with moderate PVR at discharge showing an improvement at 1 year. Based on the safety and efficacy results of this trial, the CoreValve received FDA approval for use for inoperable patients with AS in January 2014.

In the CoreValve High-Risk Study, 795 patients were randomized between February 2011 and September 2012 in the United States to receive either TAVR or SAVR.¹¹¹ In the surgical arm, 41 patients (10.2%) withdrew after randomization, leaving a total as-treated population of 747 patients (390 TAVR, 357 SAVR). Although the treatment population was older (mean age, 83.2 years), Society of Thoracic Surgeons–Predicted Risk of Mortality (STS-PROM) was lower than that seen in the PARTNER high-risk cohort (7.4% vs 11.7%). In the prespecified as-treated primary analysis, the rate of death from any cause was significantly lower with TAVR than SAVR group (14.2% vs 19.1%, $P < 0.001$ for noninferiority, one sided $P = .04$ for superiority) (Figure 29.6B). This was the first trial to demonstrate the superiority of TAVR versus SAVR in high-risk patients. Hierarchical testing of secondary endpoints showed that echocardiographic indices of valve function, quality of life, and functional status were noninferior with TAVR. Unlike in the PARTNER trial, analyses did not show any increased risk of stroke with TAVR compared with surgery. Major vascular complications and permanent pacemaker complications were more frequent in the TAVR group, and bleeding complications, AKI, and atrial fibrillation were more common in the surgical group. Based on the strength of the data from the high-risk cohort, the Medtronic CoreValve was approved for use in high-risk patients in June 2014.

SURTAVI Trial

The SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) multicenter randomized trial compared TAVR with a self-expanding valve to SAVR in intermediate surgical risk patients with AS. This study included 1660 patients (864 TAVR patients, 796 SAVR patients) in the intention to treat population. The mean STS score was $4.5\% \pm 1.6\%$. The next-generation Evolut R valve was introduced during the study and was used in 16% of patients. At 2-year follow-up, the primary composite endpoint of all-cause death or disabling stroke occurred in

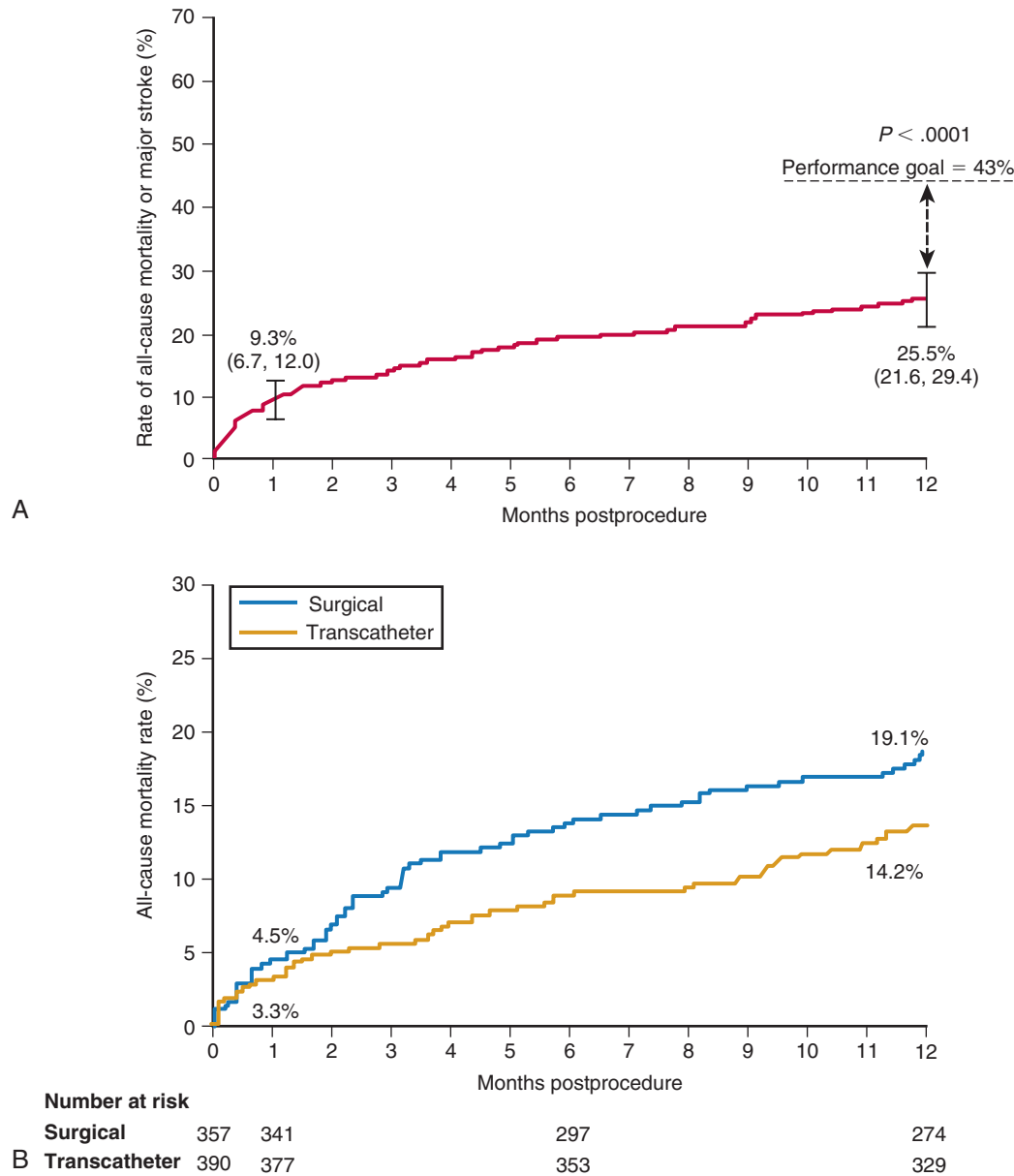


FIGURE 29.6 The 1-year CoreValve US Pivotal Trial. **A**, Cumulative hazard curve of all-cause mortality or major stroke in extreme-risk patients undergoing transfemoral aortic valve replacement (TAVR) compared with a prespecified objective performance goal. **B**, Cumulative hazard curves of all-cause mortality between high-risk patients randomized to TAVR and surgical aortic valve replacement.

12.6% of TAVR patients and 14.0% of SAVR patients (probability of noninferiority >0.999).²³ TAVR was associated with higher rates of residual PVR (5.3% vs 0.6%), major vascular complications (6.0% vs 1.1%), and new permanent pacemaker implantation (25.9% vs 6.6%) compared with SAVR. However, compared with TAVR, SAVR was associated with higher rates of AKI (1.7% vs 4.4%), atrial fibrillation (12.9% vs 43.4%), and transfusion requirements. Furthermore, at 5-year follow-up, TAVR and SAVR continued to have similar rates of all-cause mortality or disabling stroke (31.3% vs 30.8%).¹¹³ Thus, TAVR with a self-expanding valve was found to be overall noninferior compared with SAVR in the treatment of patients with severe AS at intermediate surgical risk. Thus, this study demonstrated that TAVR with a self-expanding valve was noninferior to SAVR in the treatment of patients with severe AS at intermediate surgical risk and led to the FDA expansion to intermediate-risk patients in 2017.

Evolut Low Risk Trial

Given the favorable results seen in the earlier trials using the self-expanding TAVR system in the treatment of patients with AS at high and intermediate surgical risk, the Evolut Low Risk trial sought to determine whether TAVR with a self-expanding valve in low-risk surgical AS patients was noninferior to SAVR. In this multicenter randomized study, 1468 patients were randomized to either TAVR or SAVR. An interim analysis was performed 1 year after the 850th patient underwent the study procedure²⁷ and found that TAVR with a self-expanding valve (CoreValve, Evolut R, or Evolut Pro) was noninferior to SAVR for the primary composite endpoint of death or disabling stroke at 24 months (5.3% vs 6.7%; probability of noninferiority >0.999). In addition, at 30-day follow-up, TAVR was associated with lower rates of disabling stroke (0.5% vs 1.7%), bleeding complications (2.4% vs 7.5%), AKI (0.9% vs 2.8%), and atrial fibrillation (7.7% vs 35.4%) compared with SAVR.

However, TAVR was associated with a higher incidence of moderate or severe AR (3.5% vs 0.5%) and need for new permanent pacemaker implantation (17.4% vs 6.1%). Both the TAVR and SAVR groups demonstrated improved functional improvement at 1-year follow-up. In the entire cohort, the rates of 2-year primary outcome of all-cause mortality and disabling stroke were similar between TAVR and SAVR patients (4.3% vs 6.3%; log-rank $P = .084$).¹¹⁴ Mild PVR rates continued to be higher in TAVR patients compared with SAVR patients (26.6% vs 2.6%; $P < .001$). These patients will be followed up with for 10 years to determine the long-term clinical outcomes in this patient population.

"REAL-WORLD" REGISTRIES

Several large real-world registries, often serving as national postapproval studies for specific European countries, have studied both balloon-expandable and self-expanding TAVR systems. These include the UK Transcatheter Aortic Valve Implantation (UK-TAVI), French Aortic National Corevalve and Edwards-2 (FRANCE-2), German Aortic Valve Registry (GARY), Pooled-Rotterdam-Milano-Toulouse In Collaboration (PRAGMATIC), and Transcatheter Valve Therapy (TVT) studies.¹¹⁵⁻¹¹⁹ These registries demonstrated that real-world outcomes were comparable to those seen in the randomized trials. They also helped identify and confirm the rates of important complications, including stroke, vascular complications, and bleeding as well as real-world rates of conduction abnormalities. Several key findings from these registries are as follows:

1. Mortality rates are higher with the transapical approach than with the transfemoral approach.
2. Alternative access with the subclavian approach shows nearly comparable results to the transfemoral approach.
3. Significant (moderate or greater) PVR rates are associated with worse outcomes.
4. Outcomes were similar in the real world between TAVR with either the balloon-expandable SAPIEN system or the self-expanding CoreValve system except for pacemaker rates, which were higher with CoreValve.

These registries served an important role by evaluating the outcomes of TAVR in the real world. They also fueled device iteration and set benchmarks by which centers could be evaluated as TAVR was rolled out to new centers with limited experience.

After TAVR was approved by the US FDA for the treatment of patients with high-risk AS, the STS and the ACC jointly developed a comprehensive national post-approval registry, the TVT registry,¹¹⁹ to meet a condition for Medicare coverage and to facilitate outcome assessment and comparison with other trials and international registries. This comprehensive registry database harmonized definitions from the surgical STS database and the VARC (1 and 2) initiatives and required long-term follow-up, including quality-of-life assessments. After commercial approval of the Edwards SAPIEN TAVR system, between November 2011 and May 2013, 7710 patients were enrolled at 224 participating centers in the TVT registry. The risk categories were 20% inoperable patients and 80% high-risk but still operable patients. At 30 days, in a subset with available

data (3133 patients), the first report from the TVT registry demonstrated mortality rate of 7.6%, stroke rate of 2.8%, and reintervention in 0.5% of patients. These results demonstrated that the "real-world" outcomes were reasonable and that the commercialization of TAVR was proceeding in a safe manner. Since the initial report, there have been multiple publications from TVT as different devices have been introduced and indications expanded demonstrating reasonable clinical outcomes. Although there are many limitations of large registries, the ongoing findings from the TVT registry will be useful to monitor changing patient demographics, clinical outcomes, and generalizability of TAVR in the United States.

NEW CLINICAL INDICATIONS

After TAVR had become incorporated into the armamentarium of therapies for patients with severe AS, it was predictable that many patients not included in earlier studies but who were nevertheless at high risk or not candidates for surgical valve replacement would be considered potential candidates. Thus, data are accumulating in patients with bicuspid AS, bioprosthetic valve failure, and AS and concomitant coronary disease. Similarly, after TAVR safety and durability concerns have been properly addressed, the exploration of less-invasive TAVR in lower-risk AS patients has generated considerable controversy. Importantly, the current success of TAVR has been linked to the dual pathways of careful evidence-based clinical research and technology evolution, which should continue to stimulate expansion of TAVR to new clinical indications in the future.

Bioprosthetic Valve Failure

The use of TAVR technologies to manage difficult patients with surgical bioprosthetic valve failure has been a consideration for many years. The first case using a transcatheter aortic valve via a percutaneous approach to treat a failing surgical bioprosthesis was reported in 2007 when a CoreValve self-expanding prosthesis was placed inside a degenerated surgical aortic valve in a patient at very high risk for redo SAVR.¹²⁰ Subsequently, several case series and small registries have demonstrated the feasibility and safety of transfemoral and transapical valve-in-valve implantation with both self-expanding and balloon-expandable transcatheter valves for failing bioprosthetic *aortic* valves (stenosis and regurgitation)¹²¹⁻¹²⁵ and balloon-expandable valve-in-valve and valve-in-ring for failing *mitral* bioprostheses.^{122,124-128} Moreover, case reports and small series have also emerged in high-risk patients with balloon-expandable valve treatment of failed surgical tricuspid bioprostheses.^{125,126} Three requirements for successful valve-in-valve procedures are necessary. First, an intimate understanding of the underlying surgical bioprosthesis is critical for case planning, including the internal valve dimensions (not merely the registered valve size), stented versus stentless, location of the sewing ring, valve leaflets internal or external to the valve frame, and fluoroscopic appearance. Second, advanced imaging with TEE and MSCT

is essential to best delineate anatomic details and quantitative measurements for correct valve sizing. Third, these procedures require advanced operator skills and should only be performed by the most experienced centers and operators to avoid and treat serious complications.

The largest and most comprehensive evaluation of the aortic valve-in-valve procedure are the results from the Global Valve-in-Valve registry, which evaluated 459 patients with degenerated surgical bioprosthetic aortic valves.¹²⁹ The modes of bioprosthesis failure were stenosis in 39%, regurgitation in 30%, and combined stenosis and regurgitation in 30%. At 30 days, the overall all-cause mortality rate was 7.6%, strokes were seen in 1.7% of patients, and 92% had marked symptom benefit (NYHA functional Class I or II). The overall 1-year survival rate was 83.2% with patients with AS having worse 1-year survival rates than patients with AR and patients with combined valvular disease (76.6% vs 91.2% vs 83.9%, $P = .01$).

The outcomes of a large, nested registry of high surgical risk patients with degenerated surgical aortic valves with severe AS within the PARTNER 2 trial and continued access registries were analyzed.¹³⁰ These patients were required to have a prior bioprosthesis that would be suitable for valve-in-valve treatment with either a 23- or 26-mm SAPIEN XT valve. A total of 365 patients were included in the study. At 30 days, the all-cause mortality rate was 2.7% (in comparison with STS predicted risk of surgical mortality of 9.1%), stroke was 2.7%, major vascular complication was 4.1%, coronary occlusion was 0.8%, and new pacemaker insertion was 1.9%. At 1 year, the rate of all-cause mortality was 12.4%. The mortality rates were higher in the initial registry population than in the subsequent continued access registry at 30 days (8.2% vs 0.7%; $P = .001$) and at 1 year (19.7% vs 9.8%, $P = .006$). Furthermore, this rate was lower than the rates reported in the Valve-in-Valve International Data Registry. These data may reflect improvement in outcomes as a result of increased experience with TAVR valve-in-valve implantations. In addition, this study found that valve-in-valve TAVR had lower rates of PVR (1.9% with greater than mild regurgitation), new pacemakers (1.9%), and annular rupture (0%) compared with native valve TAVR. Overall, this study found that transcatheter aortic valve-in-valve procedures were associated with low mortality and complication rates.

Transcatheter Aortic Valve Replacement for Bicuspid Aortic Valve

An area of ongoing investigation is the use of TAVR in patients with bicuspid aortic valves. The body of evidence on the long-term safety and efficacy in patients with bicuspid aortic valves is markedly limited because these patients have been uniformly excluded from TAVR trials and registries. Anatomic features intrinsic to bicuspid valves, such as annular eccentricity, high leaflet coaptation, and extensive asymmetric calcification, have led to concerns regarding the risk of TAVR, including valve dislocation, uneven prosthetic expansion, periprosthetic leaks, accelerated leaflet degeneration, coronary obstruction, and annular rupture. These adverse outcomes were reported in other types of stented valves implanted surgically,

in which adverse events were common in patients with bicuspid aortic valves but not tricuspid aortic valves.¹³¹

Nevertheless, given that recent data suggest that the rates of bicuspid valves are likely underestimated and that many of these will go on to develop valvular disease,¹³² the possibility of TAVR in this subgroup is starting to be explored. Data from single case studies and small cohorts of high and inoperable surgical risk patients have already demonstrated the feasibility of TAVR in this subset.¹³³⁻¹³⁷ Moreover, in a systematic review of the published data regarding TAVR in patients with bicuspid aortic valve, no overall differences in device success, mortality, stroke, or major vascular complications in the short or intermediate term were found compared with contemporary trials of patients with tricuspid aortic valve stenosis undergoing TAVR.¹³⁸ However, a slightly higher rate of PVR (68.5%) was noted in this study, but the vast majority was mild PVR (80%). In a study of 143 patients with bicuspid aortic valve patients undergoing TAVR, the use of CT for valve sizing compared with echocardiography alone did result in dramatically lower rates of PVR,¹³⁹ suggesting that routine use of CT in patients with bicuspid aortic valve undergoing TAVR sizing may be necessary.

A large retrospective analysis comparing outcomes of low-risk patients undergoing TAVR for bicuspid to patients with trileaflet AS was performed using data from the STS/ACC Transcatheter Valve Therapies Registry.¹⁴⁰ Patients with bicuspid AS comprised 4.4% of low-risk patients included in the registry between 2015 and 2020. The primary analysis included 3168 propensity-matched pairs of patients with bicuspid and trileaflet AS at low surgical risk and demonstrated that procedural success rates were similar between the two groups. Thirty-day mortality rates were similar between bicuspid and trileaflet patients (0.9% vs 0.8%; HR, 1.18; 95% CI, 0.68–2.03). Unlike the earlier discussed registry analysis, this study found that moderate and severe paravalvular leak were similar between bicuspid and trileaflet patients (3.4% vs 2.1%; 95% CI, -0.6 to 3.2%). Furthermore, 1-year outcomes were similar between the two groups (death: bicuspid, 4.5% vs trileaflet, 6.6%).

Thus far, the data appear to be promising for the use of TAVR in bicuspid aortic valve stenosis, but more prospective data are needed. It is important to note that the data in these registries suffers from selection bias, and many patients with bicuspid valve disease may not be appropriate for TAVR. In addition, data regarding the durability of TAVR valves is particularly important in this patient population because patients with bicuspid AS typically require intervention earlier in life than patients with trileaflet AS.

Transcatheter Aortic Valve Replacement for Native Aortic Valve Regurgitation

Although TAVR has been approved for the treatment of severe aortic valve stenosis in high-risk and inoperable patients, it is also being actively evaluated for the treatment of pure, severe native valve AR. Anatomic challenges for successful TAVR in this patient group include large annular sizes, the lack of calcification for positioning and fixation, and fairly diverse and variable aortic anatomy. Yet

despite these challenges, TAVR for native valve AR has been successfully achieved.

In an Italian multicenter study of more than 1500 patients, approximately 26 patients underwent TAVR with the CoreValve prosthesis for severe AR on the basis of compassionate use after being deemed to be at prohibitive surgical risk.¹⁴¹ Compared with patients undergoing TAVR for severe AS, the patients with severe AR had a lower rate of device success (79% vs 96%, $P = .006$), along with higher 30-day overall mortality rate (23% vs 5.9%; OR, 4.22 [3.03–8.28]; $P < .001$). In another registry of 43 patients, device success was found to be greater (97.7%), but 8 patients required a second transcatheter valve due to residual PVR. The all-cause 30-day mortality was 9.3% and was 21.4% at 12 months. Given the staggeringly poor prognosis of patients with severe AR when treated medically, TAVR with the current generation of transcatheter valves may be a reasonable alternative for inoperable patients. However, the rates of complications with the current devices are high, and newer TAVR devices, such as the JenaValve, developed specifically for the treatment of patients with AR, are under ongoing investigation.¹⁴²

COMPLICATIONS OF TRANSCATHETER AORTIC VALVE REPLACEMENT

An essential step in the developmental process and acceptance of a new treatment such as TAVR is the elucidation and management of clinically relevant therapy-associated complications. Therefore, considerable effort has been directed to the precise definitions of untoward clinical events, identifying their frequency and possible causes and reacting with subsequent procedural or technology enhancements.¹⁴³ The main complications related to TAVR are strokes, PVR, conduction abnormalities, vascular complications and bleeding, and other infrequent but extremely important events such as coronary occlusion or annulus rupture.

Stroke

Stroke remains the most feared and devastating complication associated with TAVR. At present, the 30-day frequency of clinically significant strokes after TAVR varies from 2% to 6% in different studies.^{63,64,144–146} In a large meta-analysis involving more than 10,000 patients treated with TAVR,¹⁴⁴ the frequency of both strokes and transient ischemic attacks was 3.3% at 30 days, and the associated 30-day mortality rate was 25.5% compared with 6.9% 30-day mortality rate in patients without strokes ($P < .001$). Studies have systematically demonstrated that strokes after TAVR peak in the first several days after the procedure, but delayed strokes can occur in the first 2 weeks, and late strokes (after 30 days) are frequent in this older patient population with frequent atrial fibrillation. The 1-year stroke frequencies have been 3.6% to 13.8% after TAVR in different studies and 5.2% in the large meta-analysis. Several studies have indicated that the stroke frequency after TAVR has been declining in recent years because of improved case selection, procedural technique refinements,

increased operator experience, and new TAVR systems.¹⁴⁷ There does not appear to be a significant difference in stroke frequency when comparing either balloon-expandable versus self-expanding TAVR or transapical versus transfemoral access approaches.¹⁴⁷

Although the frequency of strokes is relatively low after TAVR, subclinical brain injury is more frequent. Diffusion-weighted magnetic resonance imaging (MRI) studies after TAVR have demonstrated that up to 84% of TAVR patients have new foci of restricted diffusion, consistent with embolic lesions, and more than 75% have multiple foci.¹⁴⁸ However, despite the high frequency of new embolic lesions visualized by MRI, the vast majority of patients with these findings are asymptomatic with no overt clinical sequelae, including no decline in cognitive function, worsening quality of life, or increased 1-year mortality. Nevertheless, the neuroimaging studies are supported by recent findings indicating that macroscopic material liberated during TAVR was captured by a dual filter-based cerebral embolic protection device in 75% of the 40 patients studied.¹⁴⁹ Thrombotic material was found in 52% of patients, and tissue fragments compatible with aortic valve leaflet or aortic wall origin were also found in 52% of patients. Currently, there are three different filters or deflectors mounted on delivery catheters designed to protect the brain from intraprocedural embolic debris. Using these devices, small registries have reported some reduction in mean lesion volume after early diffusion-weighted MRI, and more definitive randomized trials are ongoing.¹⁵⁰ The multicenter Cerebral Protection in Transcatheter Aortic Valve Replacement - The SENTINEL Study (SENTINEL) trial included 363 TAVR patients randomized to either cerebral embolic protection with the Sentinel device or to no embolic protection and found no differences in stroke or neurocognitive function between the two groups or not despite embolic debris being identified within filters in 99% of patients receiving embolic protection. Clearly, there are many unanswered questions relating to stroke prevention after TAVR, including the following:

1. Impact of even lower profile TAVR devices and reduced balloon dilation (before and after TAVR)
2. Importance of perfusion deficits on neuroimaging studies and their association with sophisticated measures of neurocognitive function
3. Benefit of rigorous detection and pharmacotherapy management of new-onset atrial fibrillation
4. Value of new cerebral protection devices for either systematic or selective use during TAVR

Paravalvular Regurgitation

Unlike SAVR, in which PVR is distinctly uncommon, after either balloon-expandable or self-expanding TAVR, PVR is frequently observed because of the difficulty in achieving circumferential flush apposition of the metallic support frame with the asymmetric, distorted, and heavily calcified aortic annulus and valve leaflets. The determinants of PVR are a complex interaction of patient characteristics, procedural factors, assessment modality, and valve type. Although the reported frequency and severity of PVR after TAVR vary widely among studies, most agree that some PVR is present

in at least 50% of TAVR cases and moderate or severe PVR is present in approximately less than 10%, and rates continue to decrease.¹⁵¹⁻¹⁵⁵ The differences in reported frequency of PVR are likely due to the nonstandardized application of imaging assessment technologies (angiography vs echocardiography vs cardiac MR) and the imprecision and subjective nature of PVR severity classification schemes. Nevertheless, there is general agreement that moderate or severe PVR after TAVR is detrimental and is associated with increased subsequent mortality rates.^{151,154,156}

Differences in PVR frequency and severity among the various TAVR systems have been studied without definitive resolution.^{157,158} In a large meta-analysis including 12,926 patients, the incidence of moderate or severe PVR after CoreValve was 16.0%, whereas after SAPIEN, the incidence of PVR was 9.1% ($P < .005$).¹⁵¹ The predictors of significant PVR after TAVR were the valve implantation depth, valve undersizing, and mean Agatston calcium score.¹⁵¹ These findings underscore the three main causes of PVR:

1. Malposition of the transcatheter valve (either too high or too low), causing misalignment of the frame “seal zone” (containing the interior skirt) with the annulus
2. Undersizing the valve relative to the annulus implant dimensions
3. Severe calcification that prevents flush contact with the nondeformable support frame

Both MSCT and echocardiography studies have strongly linked PVR to the overall extent of aorta and valve calcification, asymmetric calcium distribution patterns, and vulnerable calcium locations (aortic wall, valve commissures, LVOT, and valve landing zone).¹⁵⁹⁻¹⁶¹ Optimal valve sizing has become a critical consideration in TAVR procedural planning to prevent significant PVR.^{162,163} Adjunctive imaging with 3D MSCT using standardized image acquisition protocols and analyzed with custom quantitative algorithms provide the most consistent measurements of the aortic annulus for valve sizing, including assessment of annulus geometry, major and minor axis diameters, area, and perimeter. These data are used to select the optimal valve size for a given patient, recognizing that each valve type may differ regarding sizing requirements.

The assessment of PVR after valve implantation is controversial. Most centers use a combination of hemodynamic evaluations and imaging studies (preferably both aortography and echocardiography). Arguably, intraprocedural transesophageal echocardiography, performed and analyzed by a trained specialist, is the most sensitive imaging study to determine the location and severity of PVR immediately after TAVR. Hemodynamic assessments of AR severity are also helpful, especially calculation of the dimensionless AR index⁹⁰ in patients with a stable heart rate. Also, there are data to indicate that for both the balloon-expandable and the self-expanding TAVR devices, there can be spontaneous improvement in PVR severity in the first 30 minutes after valve implantation,¹⁶⁴ which should mitigate against the immediate initiation of reparative therapies unless there is severe hemodynamic compromise. When significant PVR has developed after TAVR, there are limited treatment options. Postdilation with a carefully sized balloon has been demonstrated to be an

effective technique in reducing the degree of PVR in numerous studies,^{146,164} but the risks of increasing embolic strokes and excessive trauma to the aortic root and annulus should always be considered. In cases in which malposition of the valve causes severe PVR, placement of a second correctly located transcatheter valve (either above or below the first valve) can be curative. In the PARTNER trial, 36.1% of patients with moderate or severe PVR after the Edwards SAPIEN valve required a valve-in-valve procedure. However, the need for a second valve also resulted in a higher 1-year cardiovascular mortality rate ($P = .041$).¹⁶⁵ Last, if the PVR is persistent and clinically significant (worsening heart failure) after the index procedure, focal areas of PVR can be repaired using conventional catheter-based implantable occluder devices.

Undoubtedly, the answer to preventing PVR associated with transcatheter valves resides in meticulous assessment of the native valve anatomy with careful valve sizing using MSCT 3D imaging and advanced new TAVR designs with either subannular fixation or space-filling external materials to fill the gaps between the frame and the native valve structures.

Conduction Abnormalities and Arrhythmias

Similar to surgical aortic valve procedures, conduction disturbances occur frequently after TAVR. The pathophysiology of these new conduction disturbances is due to the superficial location of the left bundle branch in the uppermost part of the LV septum and its close proximity to the aortic valve apparatus. New-onset LBBB is the most commonly observed conduction disturbance and has been reported to vary from 29% to 65% with the CoreValve bioprosthesis and from 6% to 18% with the SAPIEN valve.^{98,102,166,167} However, approximately half of the patients who develop LBBB after TAVR have resolution by 30 days. Although one study demonstrated an association between new-onset LBBB after TAVR and increased 1-year mortality rates,¹⁰¹ multiple other studies^{102,103} have indicated similar late deaths in patients with and without new LBBB. Importantly, there have been consistent findings that new LBBB after TAVR is associated with reduced augmentation in LV function and an increased need for new pacemakers.^{102,103}

Two large meta-analyses^{168,169} have observed a 13% to 15% frequency of new pacemakers after TAVR: approximately 25% after CoreValve implantation and 6% after SAPIEN valves ($P < .001$). However, recent data suggest that the rates of CoreValve have decreased significantly, with the current iteration of the Evolut Pro rates at about 15%. There are three major predictors of new pacemakers after TAVR, including baseline right bundle branch block, low placement of the transcatheter valve, and a narrowed LVOT (or exaggerated valve oversizing). In addition, other anatomic factors such as membranous septum length also play a role. The higher frequency of pacemakers after CoreValve procedures is likely due to the longer frame length with implantation depth extending farther into the LVOT, creating augmented contact and disruption of the underlying left bundle branch tract. Studies have shown that if the depth of implantation is reduced with the CoreValve, a lower permanent pacemaker

rate can be achieved. New permanent pacemakers after TAVR have not been associated with an increased late mortality rate, but there have been increased repeat hospitalizations and reduced LV function compared with patients without new pacemakers.¹⁷⁰

New-onset atrial fibrillation has been identified in 18% to 32% of patients after TAVR,^{62,63,171} and associated predictors were moderate or severe left atrial enlargement and the transapical access route. Limited reports suggest that even brief episodes of new-onset atrial fibrillation after TAVR have been associated with an increased risk of both early and late strokes but not cardiac death.¹⁷¹ There is a clear need for more intensive patient arrhythmia monitoring after TAVR and rigorous pharmacotherapy treatment in patients with newly discovered atrial fibrillation. Other controversies that bear noting are the increasing use of cardiac resynchronization therapy after TAVR in patients with conduction disturbances and residual heart failure and the need for more sophisticated electrophysiology assessments to better determine the definite need for permanent pacemakers in patients with post-TAVR conduction disturbances.

Vascular Complications and Bleeding

From the earliest TAVR experiences, the frequent occurrence of vascular complications has tainted clinical outcomes, provoked changes in procedural techniques, and driven advances in next-generation device development. Depending on the specific definitions applied to vascular complications, the frequency has ranged from 5% to 50% in the literature. The VARC initiatives^{61,70} helped to consolidate and clarify these definitions into two main categories: (1) “major” vascular complications, which involved serious injury to the ventricle(s), aorta, or peripheral vessels (e.g., rupture, perforation, or severe dissection), resulting in compromised flow or concerning blood loss (≥ 4 units) and usually requiring either interventional or surgical corrective repair, and (2) “minor” vascular complications, which included less serious hematomas, dissections, and other vascular events that could be managed usually without deleterious long-lasting clinical outcomes.

The use of larger profile devices (>20 Fr) coupled with an unforgiving anatomic substrate (older patients with frequent peripheral vascular disease) and less experienced operators resulted in 10% to 15% major vascular complication rates in SOURCE (Edwards SAPIENTM Aortic Bioprosthesis Multi-Region Outcome Registry),⁵⁰ PARTNER,^{62,63} and an early meta-analysis.¹⁴³ In PARTNER, 15.3% of patients had major and 11.9% had minor vascular complications within 30 days, including severe dissections (62.8%), perforations (31.3%), and large access site hematoma (22.9%).⁷⁵ Major vascular complications were associated with increased major bleeding, renal failure requiring dialysis, and death at both 30 days and 1 year. The only identifiable independent predictors of major vascular complications were female sex⁷⁵ and a larger sheath-to-femoral-artery ratio.^{172,173} Over time, commensurate with increased operator experience, which resulted in the development of new procedural methods to better secure the vascular access site, and improved techniques to manage vascular complications (e.g., stent grafts)¹⁷⁴ and the

emergence of smaller sized TAVR systems,⁷⁹ the rates of both major and minor vascular complications declined significantly. Presently, in high-volume TAVR centers specializing in fully percutaneous procedures with access to modern low-profile TAVR devices, the expected frequency of major vascular complications is less than 5%. Importantly, advanced interventional skills in vascular access, closure, and complication management are absolutely necessary to achieve optimal outcomes.

The critical nature of major bleeding during interventional and surgical procedures and the association with increased subsequent mortality rates has been highlighted over the past several years. However, the incidence, need for transfusion, and long-term impact of major bleeding in the transfemoral TAVR patients decreased with lower patient risk profiles and increased operator experience. Underscoring the importance in recognizing and preventing procedure-related major bleeding, among all independent predictors of 1-year mortality in the PARTNER trial (including stroke), major bleeding events had the greatest effect on late mortality (HR, 2.36, $P < .0001$).⁷⁶ Recently, provocative reports have indicated that *late* (>30 days) bleeding after TAVR, most commonly arising from the gastrointestinal tract and amplified by the presence of atrial fibrillation, resulted in a striking increase in 1-year mortality, raising concerns that a TAVR-associated bleeding diathesis perhaps combined with the effects of adjunctive pharmacotherapy must be further explored in the future.

Other Less Frequent Complications

There are several rare, but nonetheless clinically important, complications associated with TAVR. Among this group of less frequent complications, the two that deserve special mention are coronary artery obstruction and aortic root rupture. Coronary obstruction during TAVR is a rare but dreaded complication caused by displacement of the native aortic valve leaflets into the coronary ostia, resulting in obstruction of flow with associated clinical sequelae. In a large multicenter TAVR registry (6688 patients), there were 44 cases (0.66%) of symptomatic coronary obstruction.¹⁷⁵ Baseline and procedural variables associated with coronary obstruction were older age, female sex, no previous coronary artery bypass graft, the use of a balloon-expandable valve, and previous surgical aortic bioprosthesis. The left coronary artery was the most commonly involved (88.6%), and both low-lying coronary ostia and narrowed sinus of Valsalva diameter were associated anatomic factors. Most patients presented with persistent severe hypotension (68.2%) and electrocardiographic changes (56.8%). Percutaneous coronary intervention was attempted in 75% of these cases (successful in 81.8%), and the 30-day mortality rate was 40.9%. Identifying patients at high risk for coronary obstruction based on the MSCT is critical to preventing this complication. This can be done by “implanting” a virtual valve and measuring the distance from the prosthesis to the native coronary (Virtual THV-C distance).¹⁷⁶ A distance less than 4 mm, especially with a low left main coronary artery, identifies high-risk patients. In high-risk cases (low-lying coronaries and narrowed sinuses), many operators are “protecting” the coronary ostia with placement of guidewires, balloons, and even stents,

which can be deployed immediately if coronary obstruction is observed. Another option that has recently been used is electrosurgery to lacerate the native leaflet in front of the coronary to prevent it from obstructing flow. This procedure, termed BASILICA (Bioprosthetic or Native Aortic Scallop Intentional Laceration to Prevent Iatrogenic Coronary Artery Obstruction), remains complex and requires experienced operators, resulting in limited use currently.¹⁷⁷

Another rare but potentially devastating complication during TAVR is either contained or noncontained rupture of the LVOT, annulus, or aorta. An analysis of anatomic and procedural features of 31 consecutive ruptures (of which 11 were contained periaortic hematomas) associated with balloon-expandable TAVR was compiled from 16 centers.¹⁷⁸ Patients with root rupture had a higher degree of subannular or outflow tract calcification, a higher frequency of 20% or greater annular area valve oversizing, and more frequent balloon postdilation. The typical phenotype of a rupture-prone TAVR patient is a frail woman with a low body mass index who has a heavily calcified aorta and narrowed or effaced aortic sinuses who is and receiving chronic corticosteroid therapy. Aortic rupture occurs more frequently with balloon-expandable compared with self-expanding TAVR systems. Most cases of noncontained aortic rupture result in immediate or progressive hemodynamic collapse, requiring emergency pericardiocentesis and open surgical repair, usually with poor short-term survival.

One other late complication that is worth nothing is transcatheter valve leaflet thrombosis. Several case reports of late (2–12 months after the index procedure) valve thrombosis initially described the phenomenon,^{179,180} wherein premature impaired leaflet motion and elevated aortic valve gradients mimicking early structural valve deterioration have responded to chronic systemic anticoagulation using warfarin with normalized leaflet motion. A systemic analysis from the Portico Re-sheathable Transcatheter Aortic Valve System US IDE (PORTICO) trial combined with several registries from Europe published in 2015 was the first to demonstrate that this phenomenon of leaflet thickening, termed HALT (hypoattenuated leaflet thickening), can occur with frequencies as high as 40%.¹⁸¹ HALT can result in abnormal leaflet motion termed HAM (hypoattenuation affecting motion). This phenomenon was subsequently investigated in the low-risk TAVR studies with SAPIEN 3 and Evolut R, which incorporated dedicated CT substudies at 30 days and 1 year.^{182,183} Based on these, the phenomenon of HALT and HAM can be described in the following manner:

1. HALT is a frequent phenomenon with rates at 20% to 30% at 1 year.
2. HALT is a dynamic phenomenon with spontaneous resolution.
3. Clinically relevant HAM is rare with significant valve dysfunction rates in the low single digits.

The prevention and management of leaflet thrombosis remains an important area of ongoing investigation. It is clearly not just an imaging phenomenon, but the clinical relevance remains unclear. Trials investigating routine anticoagulation demonstrated lower rates of HALT but at a cost of increased bleeding and worse survival.¹⁸⁴ More investigation into identifying risk factors and developing prosthesis at lower risk for HALT are ongoing and will hopefully result in improved clinical outcomes.

NEW TRANSCATHETER AORTIC VALVE REPLACEMENT DEVICES

Overview

Despite the success of “first-generation” TAVR systems, several device design limitations have been identified that contributed to suboptimal clinical outcomes. Previously, large-diameter TAVR delivery sheaths created a significant femoral artery-sheath size mismatch in many patients, resulting in major vascular complications and the frequent use of nontransfemoral access sites. In the future, to safely support successful transfemoral access in the vast majority of TAVR-eligible patients (especially women), an outer sheath diameter of less than 18 Fr for all valve sizes is advisable. Smaller TAVR system profiles are also important to negotiate tortuous vascular anatomy, facilitate native valve crossing, minimize trauma to the aorta and the native valve, allow the option of no predilation before deployment, and improve alignment and positioning accuracy during implantation. Another important limitation of early and current TAVR systems is the lack of consistent and precise positioning of the valve at the ideal landing zone, which has resulted in valve malpositioning, obstruction of the coronary arteries (too high placement), interference with the conduction system or the mitral valve (too low placement), and increased PVR (either too high or too low placement). Ideally, a slow and controlled valve deployment, allowing for positioning adjustments before final implantation, is preferred. The availability of partial or complete valve retrieval has been incorporated into many of the newer self-expanding TAVR systems, which provides the operator a “second chance” if the initial attempts at precise positioning were suboptimal. One of the greatest differences between SAVR and TAVR has been the increased frequency and severity of PVR. To address this issue, newer TAVR devices have explored improvements in subannular fixation and coaxial alignment, as well as the addition of external space-filling materials to reduce or eliminate incomplete circumferential apposition of the valve frame against the aortic annulus. Finally, the durability of the frame and valve itself remains a concern, especially if long-term implants in younger patients are being contemplated. In addition to the balloon-expandable SAPIEN 3 and the self-expanding CoreValve EVOLUT R, other new TAVR systems, which are currently available or in early-stage clinical investigations, have attempted to address many of the aforementioned design limitations (see [Figure 29.3](#)).

Self-Expanding Transcatheter Aortic Valve Replacement Systems

Most of the new TAVR devices have features of a self-expanding support frame composed of nitinol and deployed using a sheath retraction system.

PORTICO (St. Jude's Medical) is a recently introduced “long frame” self-expanding TAVR system (see [Figure 29.3C](#)). Although similar in some respects to CoreValve, differentiating features include an intraannular bovine pericardial valve with a lower porcine pericardial sealing cuff, larger stent cells to improve anatomic conformation and coronary access, and complete retrievability of the valve during deployment. A total of 83 patients were studied in six European

centers using the transfemoral system with favorable clinical outcomes, good valve hemodynamics, lower than expected new pacemakers (10.8%), and infrequent moderate or severe PVR (5%).¹⁸⁵ The PORTICO IDE (Portico Resheathable Transcatheter Aortic Valve System US Investigational Device Exemption) trial was a multicenter noninferiority trial that randomized 750 high- and extreme-risk patients with AS to either treatment with TAVR with the first-generation Portico valve or to a commercially available valve.¹⁸⁶ The Portico valve had higher rates of the 30-day primary safety endpoint (composite of all-cause mortality, disabling stroke, life-threatening bleeding requiring transfusion, AKI requiring dialysis, or major vascular complication), albeit noninferior rates, compared with commercially available valves (13.8% vs 9.6%; 95% CI, -0.4 to 8.8; $p_{\text{non-inferiority}} = .034$). However, at 1 year, the Portico valve group and the commercial valve group had similar rates of the primary efficacy endpoint (composite of all-cause mortality or disabling stroke; 14.8% vs 13.4%; 95% CI, -3.6 to 6.5; $p_{\text{noninferiority}} = .0058$). Notably, patients treated with the Portico valve had higher rates of moderate or severe PVR at 1 year (7.8% vs 1.5%; $P = .0005$). The next-generation Portico NG (Navitor) valve with an external skirt and second-generation FlexNav Delivery system are currently being evaluated in a clinical trial.

The ACURATE (Symetis) valve (see Figure 29.3D) consists of stabilizing arches in the aorta to maintain coaxial alignment, a supraannular porcine pericardial valve within a self-expanding upper crown, and a contoured lower crown encircled by a fabric skirt that can be partially resheathed. The commissures of the stent have a circular radiopaque appearance, which facilitates commissural alignment with the native valve. The lower portion of the frame tends to self-adjust to the geometry of the annulus, which creates a subannular fixation zone to reduce PVR. The 28-Fr transapical TA Acurate system was studied in 40 patients with excellent results; low mortality, low PVR, and infrequent need for new pacemakers,¹⁸⁷ and the transfemoral version were evaluated in five centers in Brazil and Germany in 80 patients with similar favorable outcomes.¹⁸⁸ The transfemoral ACURATE neo TAVR system was compared with the S3 TAVR system in the SCOPE (Safety and Efficacy comparison of Two TAVI systems in a Prospective Randomized Evaluation) I multicenter, randomized noninferiority trial.¹⁸⁹ A total of 739 patients were enrolled (372 to ACURATE neo and 364 to SAPIEN 3). The ACURATE neo group failed to meet noninferiority for the 30-day primary safety and endpoint composite of all-cause death, any stroke, life-threatening or disabling bleeding, major vascular complications, coronary artery obstruction requiring intervention, AKI, rehospitalization for valve-related symptoms of congestive heart failure, valve-related dysfunction requiring repeat procedure, moderate or severe prosthetic valve regurgitation, or prosthetic valve stenosis compared with the SAPIEN 3 group (24% vs 16%; upper 95% confidence limit, 12.0%; $P = .42$). Similarly, in the SCOPE 2 trial comparing the ACURATE neo valve with the CoreValve Evolut valve, the ACURATE neo valve did not meet noninferiority compared with the CoreValve Evolut valve for the primary endpoint of all-cause death or stroke at 1 year (15.8% vs 13.9%; upper one-sided 95% confidence limit, 6.1%; $P = .0549$).¹⁹⁰

ACURATE neo2 is the latest iteration of this valve with improvements to potentially improve its clinical performance. There is a new annular sealing technology designed to conform to irregular calcified anatomies to decrease PVR. The new iSLEEVE expandable introducer has also been created to allow for low-profile vascular and sheath expansion during valve insertion. This valve and system is currently undergoing clinical investigation.

Other Transcatheter Aortic Valve Replacement Concepts

The JenaValve (JenaValve) consists of a short self-expanding nitinol frame housing a valve derived from porcine valve material with a porcine pericardial skirt and an upper crown for stabilization. Arms or “feelers” are positioned behind the native valve leaflets, allowing “clipping” of the valve against the lower stent (see Figure 29.3E). When ideally positioned, there is correct commissural alignment, sparing of the coronary arteries, and an intraannular position, which avoids the conduction system. The JUPITER (The JenaValve Evaluation of Long Term Performance and Safety In PaTients With SEvere Aortic Stenosis oR Aortic Insufficiency) multicenter study in 126 patients, all with transapical access, showed a very low mortality rate and stroke rate, rare PVR, and rare new pacemakers.¹⁹¹ This device has also been used for patients with predominant AR in a small registry.¹⁴² A transfemoral version of the JenaValve underwent an early feasibility study evaluating its safety and effectiveness in treating patients with severe AS.¹⁹² A total of 15 patients were enrolled and had a mean STS score of $5.5\% \pm 4.6$. The primary endpoint of all-cause death occurred in zero patients at 30-day and 3-month follow-up. In addition, there were no patients with moderate or severe PVR, and no new permanent pacemakers were required. In addition, this system was evaluated in 12 patients with severe AR in an early feasibility study.¹⁹³ Technical success was achieved in 92% of patients. There were no deaths at 30 days. These data are encouraging, but larger clinical trials are required to determine the safety and effectiveness of this valve in the treatment of patients with AS or AR. The ALIGN-AR (A Study to Assess Safety and Effectiveness of the JenaValve Trilogy™ Heart Valve System in the Treatment of High Surgical Risk Patients With Symptomatic, Severe Aortic Regurgitation) Pivotal Trial to evaluate the use of the transfemoral JenaValve system in the treatment of high-risk patients with symptomatic severe AR.

FUTURE DIRECTIONS

Transcatheter aortic valve replacement is a breakthrough new technology platform that has expanded the armamentarium of therapies for patients with AS, especially those who are at high risk for conventional surgery. The multidisciplinary heart valve team serves as the central vehicle for determining appropriate case selection and directing care for these patients. Thus far, impressive clinical research validation of TAVR has been established via RCTs and careful registries.

Despite the impressive growth of TAVR, there are many challenges as well as future opportunities for expanding clinical applications and improving patient outcomes. Ultimately, the role of this less-invasive form of valve replacement will depend on three unresolved issues:

1. Equivalence or superiority compared with surgery of major clinical endpoints, particularly death and stroke, for designated study populations
2. Further reduction of TAVR procedure-related major complications (e.g., PVR, vascular and bleeding events)
3. Valve durability similar to surgical bioprostheses

If these issues can be resolved in favor of TAVR, it is possible that TAVR could become the preferred therapy for treating aortic valve disease in a growing population. Exceptions might be based on anatomic considerations, such as true bicuspid aortic valves, AS with concomitant severe coronary disease or other valve lesions, and vascular access contraindications. Patients with other clinical scenarios such as surgical bioprosthesis failure (aortic and mitral), severe asymptomatic AS, and low-flow-low-gradient AS might also benefit from a less-invasive valve replacement strategy.

Other procedural enhancements may include reducing the need for either predilation or postdilation, cerebral protection to decrease strokes, improved online adjunctive imaging to refine valve positioning, and reducing the need for general anesthesia. Combined procedures with TAVR—coronary angioplasty, left atrial appendage closure, or MitraClip edge-to-edge repair for residual moderate or severe MR—are also currently under investigation. Finally, improved adjunctive pharmacotherapy strategies after TAVR require careful exploration in the form of thoughtful clinical trials.

CONCLUSIONS

Clearly, the explosion of new TAVR technology, including worthwhile iterations of first-generation devices to improve PVR and positioning, has been a major contributor to improved clinical results. One can easily imagine a time in the near future when 3D bioprinting of the diseased native valve generates true anatomic models for precise case planning experiences to optimize choices of the most appropriate valve designs and sizes for a given patient. The pioneering spirit and vision of Alain Cribier more than a decade ago to provide a new catheter-based alternative treatment for AS has been realized with lofty expectations that future evolution and maturation will render TAVR as the preferred standard therapy for the majority of patients with severe AS.

REFERENCES

1. Cribier A, Savin T, Saoudi N, Rocha P, Berland J, Letac B. Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: an alternative to valve replacement? *Lancet*. 1986;1:63-67.
2. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation*. 2002;106:3006-3008.
3. Sakata Y, Syed Z, Salinger MH, Feldman T. Percutaneous balloon aortic valvuloplasty: antegrade transseptal vs. conventional retrograde transarterial approach. *Catheter Cardiovasc Interv*. 2005;64:314-321.
4. Percutaneous balloon aortic valvuloplasty. Acute and 30-day follow-up results in 674 patients from the NHLBI Balloon Valvuloplasty Registry. *Circulation*. 1991;84:2383-2397.
5. Otto CM, Mickel MC, Kennedy JW, et al. Three-year outcome after balloon aortic valvuloplasty. Insights into prognosis of valvular aortic stenosis. *Circulation*. 1994;89:642-650.
6. McKay RG. The Mansfield Scientific Aortic Valvuloplasty Registry: overview of acute hemodynamic results and procedural complications. *J Am Coll Cardiol*. 1991;17:485-491.
7. Ben-Dor I, Pichard AD, Satler LF, et al. Complications and outcome of balloon aortic valvuloplasty in high-risk or inoperable patients. *JACC Cardiovasc Interv*. 2010;3:1150-1156.
8. Eltchaninoff H, Durand E, Borz B, et al. Balloon aortic valvuloplasty in the era of transcatheter aortic valve replacement: acute and long-term outcomes. *Am Heart J*. 2014;167:235-240.
9. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143:e35-e71.
10. Kolte D, Khera S, Vemulapalli S, et al. Outcomes following urgent/emergent transcatheter aortic valve replacement: insights from the STS/ACC TVT Registry. *JACC Cardiovasc Interv*. 2018;11:1175-1185.
11. Szerlip M, Arsalan M, Mack MC, et al. Usefulness of balloon aortic valvuloplasty in the management of patients with aortic stenosis. *Am J Cardiol*. 2017;120:1366-1372.
12. Bongiovanni D, Kühl C, Bleiziffer S, et al. Emergency treatment of decompensated aortic stenosis. *Heart*. 2018;104:23-29.
13. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43(7):561-632.
14. Leon M. A review of new aortic valvuloplasty systems: *InterValve*, *Loma Vista*, *CardioSculpt*, and *Pi-Cardia*. Transcatheter Cardiovascular Therapeutics 25th Annual Scientific Symposium. 2013.
15. Woitek F. Perfusion-balloon valvuloplasty facilitating TAVR without rapid pacing: the TRUE-FLOW study. Transcatheter Cardiovascular Therapeutics. 2017.
16. Davies H. Catheter-mounted valve for temporary relief of aortic insufficiency. *Lancet*. 1965;1:250.
17. Andersen HR, Knudsen LL, Hasenkam JM. Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs. *Eur Heart J*. 1992;13:704-708.
18. Bonhoeffer P, Boudjemline Y, Saliba Z, et al. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. *Lancet*. 2000;356:1403-1405.
19. Leon MB, Gada H, Fontana GP. Challenges and future opportunities for transcatheter aortic valve therapy. *Prog Cardiovasc Dis*. 2014;56:635-645.
20. Thyregod HG, Steinbrüchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *J Am Coll Cardiol*. 2015;65:2184-2194.
21. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609-1620.
22. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet*. 2016;387:2218-2225.
23. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376:1321-1331.
24. Makkar RR, Thourani VH, Mack MJ, et al. Five-year outcomes of transcatheter or surgical aortic-valve replacement. *N Engl J Med*. 2020;382:799-809.
25. Siontis GC, Praz F, Pilgrim T, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. *Eur Heart J*. 2016;37:3503-3512.
26. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695-1705.
27. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380:1706-1715.
28. Leon MB, Mack MJ, Hahn RT, et al. Outcomes 2 years after transcatheter aortic valve replacement in patients at low surgical risk. *J Am Coll Cardiol*. 2021;77:1149-1161.
29. Nashef SA, Roques F, Hammill BG, et al. Validation of European System for Cardiac Operative Risk Evaluation (EuroSCORE) in North American cardiac surgery. *Eur J Cardiothorac Surg*. 2002;22:101-105.
30. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2—isolated valve surgery. *Ann Thorac Surg*. 2009;88(suppl):S23-S42.
31. Edwards FH, Cohen DJ, O'Brien SM, et al. Development and validation of a risk prediction model for in-hospital mortality after transcatheter aortic valve replacement. *JAMA Cardiol*. 2016;1:46-52.
32. Hyman MC, Vemulapalli S, Szeto WY, et al. Conscious sedation versus general anesthesia for transcatheter aortic valve replacement: insights from the National Cardiovascular Data Registry Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. *Circulation*. 2017;136:2132-2140.

33. Iannaccone A, Marwick TH. Cost effectiveness of transcatheter aortic valve replacement compared with medical management or surgery for patients with aortic stenosis. *Appl Health Econ Health Policy*. 2015;13:29-45.
34. Lauck SB, Baron SJ, Sathananthan J, et al. Exploring the reduction in hospitalization costs associated with next-day discharge following transfemoral transcatheter aortic valve replacement in the United States. *Structural Heart*. 2019;3:423-430.
35. Babaliaros V, Devireddy C, Lerakis S, et al. Comparison of transfemoral transcatheter aortic valve replacement performed in the catheterization laboratory (minimalist approach) versus hybrid operating room (standard approach): outcomes and cost analysis. *JACC Cardiovasc Interv*. 2014;7:898-904.
36. Lauck SB, Wood DA, Baumbusch J, et al. Vancouver transcatheter aortic valve replacement clinical pathway: minimalist approach, standardized care, and discharge criteria to reduce length of stay. *Circ Cardiovasc Qual Outcomes*. 2016;9:312-321.
37. Cribrier A, Eltchaninoff H, Tron C, et al. Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis. *J Am Coll Cardiol*. 2004;43:698-703.
38. Webb JG, Chandavimol M, Thompson CR, et al. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation*. 2006;113:842-850.
39. Rheude T, Pellegrini C, Lutz J, et al. Transcatheter aortic valve replacement with balloon-expandable valves: comparison of SAPIEN 3 Ultra versus SAPIEN 3. *JACC Cardiovasc Interv*. 2020;13:2631-2638.
40. Class 1 Device Recall Edwards SAPIEN 3 Ultra Delivery System.
41. Kasel AM, Casese S, Leber AW, von Scheidt W, Kastrati A. Fluorocopy-guided aortic root imaging for TAVR: "follow the right cusp" rule. *JACC Cardiovasc Imaging*. 2013;6:274-275.
42. Sharp AS, Michev I, Maisano F, et al. A new technique for vascular access management in transcatheter aortic valve implantation. *Catheter Cardiovasc Interv*. 2010;75:784-793.
43. Lichtenstein SV, Cheung A, Ye J, et al. Transapical transcatheter aortic valve implantation in humans: initial clinical experience. *Circulation*. 2006;114:591-596.
44. Van Mieghem NM, Lüthen C, Oei F, et al. Completely percutaneous transcatheter aortic valve implantation through transaxillary route: an evolving concept. *EuroIntervention*. 2012;7:1340-1342.
45. Kodali SK, O'Neill WW, Moses JW, et al. Early and late (one year) outcomes following transcatheter aortic valve implantation in patients with severe aortic stenosis (from the United States REVIVAL trial). *Am J Cardiol*. 2011;107:1058-1064.
46. Lefèvre T, Kappetein AP, Wolner E, et al. One year follow-up of the multicentre European PARTNER transcatheter heart valve study. *Eur Heart J*. 2011;32:148-157.
47. Svensson LG, Dewey T, Kapadia S, et al. United States feasibility study of transcatheter insertion of a stented aortic valve by the left ventricular apex. *Ann Thorac Surg*. 2008;86:46-54; discussion 54-55.
48. Walther T, Kasimir MT, Doss M, et al. One-year interim follow-up results of the TRAVERSE trial: the initial feasibility study for trans-apical aortic-valve implantation. *Eur J Cardiothorac Surg*. 2011;39:532-537.
49. Thomas M, Schymik G, Walther T, et al. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation*. 2011;124:425-433.
50. Thomas M, Schymik G, Walther T, et al. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation*. 2010;122:62-69.
51. Wendler O, Walther T, Nataf P, et al. Trans-apical aortic valve implantation: univariate and multivariate analyses of the early results from the SOURCE registry. *Eur J Cardiothorac Surg*. 2010;38:119-127.
52. Wendler O, Walther T, Schroefel H, et al. Transapical aortic valve implantation: mid-term outcome from the SOURCE registry. *Eur J Cardiothorac Surg*. 2013;43:505-511; discussion 511-512.
53. Rodés-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol*. 2010;55:1080-1090.
54. Rodés-Cabau J, Webb JG, Cheung A, et al. Long-term outcomes after transcatheter aortic valve implantation: insights on prognostic factors and valve durability from the Canadian multicenter experience. *J Am Coll Cardiol*. 2012;60:1864-1875.
55. Piazza N, Grube E, Gerckens U, et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) CoreValve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. *EuroIntervention*. 2008;4:242-249.
56. Sack S. The PREVAIL XT (TF and TA) Registries. Transcatheter Cardiovascular Therapeutics 24th Annual Scientific Symposium. 2012.
57. Thomas M. The SOURCE Multicenter EU Registries (including XT. Transcatheter Cardiovascular Therapeutics 24th Annual Scientific Symposium. 2012.
58. Walther T, Thielmann M, Kempfert J, et al. PREVAIL TRANSAPICAL: multicentre trial of transcatheter aortic valve implantation using the newly designed bioprosthesis (SAPIEN-XT) and delivery system (ASCENDRA-II). *Eur J Cardiothorac Surg*. 2012;42:278-283; discussion 283.
59. Walther T, Thielmann M, Kempfert J, et al. One-year multicentre outcomes of transapical aortic valve implantation using the SAPIEN XT™ valve: the PREVAIL transapical study. *Eur J Cardiothorac Surg*. 2013;43:986-992.
60. Schymik G, Lefèvre T, Bartorelli AL, et al. European experience with the second-generation Edwards SAPIEN XT transcatheter heart valve in patients with severe aortic stenosis: 1-year outcomes from the SOURCE XT Registry. *JACC Cardiovasc Interv*. 2015;8:657-669.
61. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol*. 2011;57:253-269.
62. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597-1607.
63. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187-2198.
64. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med*. 2012;366:1696-1704.
65. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med*. 2012;366:1686-1695.
66. Kapadia SR, Tuzcu EM, Makkar RR, et al. Long-term outcomes of inoperable patients with aortic stenosis randomly assigned to transcatheter aortic valve replacement or standard therapy. *Circulation*. 2014;130:1483-1492.
67. Thourani V. Three-year outcomes after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis. American College of Cardiology Annual Scientific Session. 2013.
68. Kapadia SR, Leon MB, Makkar RR, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2485-2491.
69. Abdel-Wahab M, Mehilli J, Frerker C, et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. *JAMA*. 2014;311:1503-1514.
70. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg*. 2012;42(suppl):S45-S60.
71. Généreux P, Piazza N, Alu MC, et al. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol*. 2021;77:2717-2746.
72. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477-2484.
73. Reynolds MR, Magnuson EA, Lei Y, et al. Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. *Circulation*. 2011;124:1964-1972.
74. Reynolds MR, Magnuson EA, Wang K, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of Aortic Transcatheter Valve) Trial (Cohort A). *J Am Coll Cardiol*. 2012;60:548-558.
75. Généreux P, Webb JG, Svensson LG, et al. Vascular complications after transcatheter aortic valve replacement: insights from the PARTNER (Placement of Aortic Transcatheter Valve) trial. *J Am Coll Cardiol*. 2012;60:1043-1052.
76. Généreux P, Cohen DJ, Williams MR, et al. Bleeding complications after surgical aortic valve replacement compared with transcatheter aortic valve replacement: insights from the PARTNER I Trial (Placement of Aortic Transcatheter Valve). *J Am Coll Cardiol*. 2014;63:1100-1109.
77. Williams M, Kodali SK, Hahn RT, et al. Sex-related differences in outcomes after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis: insights from the PARTNER Trial (Placement of Aortic Transcatheter Valve). *J Am Coll Cardiol*. 2014;63:1522-1528.
78. Barbanti M, Webb JG, Hahn RT, et al. Impact of preoperative moderate/severe mitral regurgitation on 2-year outcome after transcatheter and surgical aortic valve replacement: insight from the Placement of Aortic Transcatheter Valve (PARTNER) Trial Cohort A. *Circulation*. 2013;128:2776-2784.
79. Webb JG, Doshi D, Mack MJ, et al. A randomized evaluation of the SAPIEN XT transcatheter heart valve system in patients with aortic stenosis who are not candidates for surgery. *JACC Cardiovasc Interv*. 2015;8:1797-1806.
80. Pibarot P, Hahn RT, Weissman NJ, et al. Association of paravalvular regurgitation with 1-year outcomes after transcatheter aortic valve replacement with the SAPIEN 3 valve. *JAMA Cardiol*. 2017;2:1208-1216.
81. Pibarot P, Ternacle J, Jaber WA, et al. Structural deterioration of transcatheter versus surgical aortic valve bioprostheses in the PARTNER-2 trial. *J Am Coll Cardiol*. 2020;76:1830-1843.
82. Lal P, Upasani P, Kanwar S, et al. First-in-man experience of percutaneous aortic valve replacement using self-expanding CoreValve prosthesis. *Indian Heart J*. 2011;63:241-244.
83. Grube E, Laborde JC, Gerckens U, et al. Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study. *Circulation*. 2006;114:1616-1624.
84. Grube E, Schuler G, Buellesfeld L, et al. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and

- current third-generation self-expanding CoreValve prosthesis: device success and 30-day clinical outcome. *J Am Coll Cardiol*. 2007;50:69-76.
85. Piazza N, Martucci G, Lachapelle K, et al. First-in-human experience with the Medtronic CoreValve Evolut R. *EuroIntervention*. 2014;9:1260-1263.
 86. Oguri A, Yamamoto M, Mouillet G, et al. Clinical outcomes and safety of transfemoral aortic valve implantation under general versus local anesthesia: subanalysis of the French Aortic National CoreValve and Edwards 2 registry. *Circ Cardiovasc Interv*. 2014;7:602-610.
 87. Tang GHL, Zaid S, Michev I, et al. "Cusp-overlap" view simplifies fluoroscopy-guided implantation of self-expanding valve in transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2018;11:1663-1665.
 88. Ben-Shoshan J, Alosaimi H, Lauzier PT, et al. Double S-curve versus cusp-overlap technique: defining the optimal fluoroscopic projection for TAVR with a self-expanding device. *JACC Cardiovasc Interv*. 2021;14:185-194.
 89. Grube E, Nabar C, Abizaid A, et al. Feasibility of transcatheter aortic valve implantation without balloon pre-dilation: a pilot study. *JACC Cardiovasc Interv*. 2011;4:751-757.
 90. Sinning J-M, Hammerstingl C, Vasa-Nicotera M, et al. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2012;59:1134-1141.
 91. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2009;22:975-1014; quiz 1082-1084.
 92. Moynagh AM, Scott DJ, Baumbach A, et al. CoreValve transcatheter aortic valve implantation via the subclavian artery: comparison with the transfemoral approach. *J Am Coll Cardiol*. 2011;57:634-635.
 93. Reardon MJ, Adams DH, Coselli JS, et al. Self-expanding transcatheter aortic valve replacement using alternative access sites in symptomatic patients with severe aortic stenosis deemed extreme risk of surgery. *J Thorac Cardiovasc Surg*. 2014;148:2869-2876.e1-e7.
 94. Fiorina C, Barbanti M, De Carlo M, et al. One year clinical outcomes in patients with severe aortic stenosis and left ventricular systolic dysfunction undergoing transcatheter aortic valve implantation: results from the Italian CoreValve Registry. *Int J Cardiol*. 2013;168:4877-4879.
 95. Barbanti M, Ussia GP, Cannata S, Giarratana A, Sgroi C, Tamburino C. 3-year outcomes of self-expanding CoreValve prosthesis—the Italian Registry. *Ann Cardiothorac Surg*. 2012;1:182-184.
 96. Meredith IT, Walton A, Walters DL, et al. Mid-term outcomes in patients following transcatheter aortic valve implantation in the CoreValve Australia and New Zealand Study. *Heart Lung Circ*. 2015;24:281-290.
 97. Linke A, Wenaweser P, Gerckens U, et al. Treatment of aortic stenosis with a self-expanding transcatheter valve: the International Multi-centre ADVANCE Study. *Eur Heart J*. 2014;35:2672-2684.
 98. Khawaja MZ, Rajani R, Cook A, et al. Permanent pacemaker insertion after CoreValve transcatheter aortic valve implantation: incidence and contributing factors (the UK CoreValve Collaborative). *Circulation*. 2011;123:951-960.
 99. Testa L, Latib A, De Marco F, et al. Clinical impact of persistent left bundle-branch block after transcatheter aortic valve implantation with CoreValve Revalving System. *Circulation*. 2013;127:1300-1307.
 100. Franzoni I, Latib A, Maisano F, et al. Comparison of incidence and predictors of left bundle branch block after transcatheter aortic valve implantation using the CoreValve versus the Edwards valve. *Am J Cardiol*. 2013;112:554-559.
 101. Houthuizen P, Van Garsse LA, Poels TT, et al. Left bundle-branch block induced by transcatheter aortic valve implantation increases risk of death. *Circulation*. 2012;126:720-728.
 102. Nazif TM, Williams MR, Hahn RT, et al. Clinical implications of new-onset left bundle branch block after transcatheter aortic valve replacement: analysis of the PARTNER experience. *Eur Heart J*. 2014;35:1599-1607.
 103. Urena M, Mok M, Serra V, et al. Predictive factors and long-term clinical consequences of persistent left bundle branch block following transcatheter aortic valve implantation with a balloon-expandable valve. *J Am Coll Cardiol*. 2012;60:1743-1752.
 104. van der Boon RM, Nuis R-J, Van Mieghem NM, et al. New conduction abnormalities after TAVI—frequency and causes. *Nat Rev Cardiol*. 2012;9:454-463.
 105. Buellesfeld L, Stortecky S, Heg D, et al. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2012;60:493-501.
 106. De Carlo M, Giannini C, Bedogni F, et al. Safety of a conservative strategy of permanent pacemaker implantation after transcatheter aortic CoreValve implantation. *Am Heart J*. 2012;163:492-499.
 107. Popma JJ, Reardon MJ, Khabbaz K, et al. Early clinical outcomes after transcatheter aortic valve replacement using a novel self-expanding bioprosthesis in patients with severe aortic stenosis who are suboptimal for surgery: results of the Evolut R U.S. study. *JACC Cardiovasc Interv*. 2017;10:268-275.
 108. Hellhammer K, Playda K, Afzal S, et al. The latest evolution of the Medtronic CoreValve system in the era of transcatheter aortic valve replacement: matched comparison of the Evolut PRO and Evolut R. *JACC Cardiovasc Interv*. 2018;11:2314-2322.
 109. Forrest JK, Mangi AA, Popma JJ, et al. Early outcomes with the Evolut PRO repositionable self-expanding transcatheter aortic valve with pericardial wrap. *JACC Cardiovasc Interv*. 2018;11:160-168.
 110. Manoharan G, Grube E, Van Mieghem NM, et al. Thirty-day clinical outcomes of the Evolut PRO self-expanding transcatheter aortic valve: the international FORWARD PRO study. *EuroIntervention*. 2020;16:850-857.
 111. Adams DH, Popma JJ, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;371:967-968.
 112. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol*. 2014;63:1972-1981.
 113. Van Mieghem N. 5-year clinical and echocardiographic outcomes from the randomized SURTAVI Trial. *Transcatheter Cardiovascular Therapeutics*. 2021.
 114. Forrest JK. Complete 2-year follow-up from the Evolut low risk trial [Presented at a meeting in Paris]. *EuroPCR*; 2021.
 115. Moat NE, Ludman P, de Belder MA, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol*. 2011;58:2130-2138.
 116. Gilard M, Eltchaninoff H, Iung B, et al. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med*. 2012;366:1705-1715.
 117. Beckmann A, Hamm C, Figulla HR, et al. The German Aortic Valve Registry (GARY): a nationwide registry for patients undergoing invasive therapy for severe aortic valve stenosis. *Thorac Cardiovasc Surg*. 2012;60:319-325.
 118. Chieffo A, Buchanan GL, Van Mieghem NM, et al. Transcatheter aortic valve implantation with the Edwards SAPIEN versus the Medtronic CoreValve revalving system devices: a multicenter collaborative study: the PRAGMATIC Plus Initiative (Pooled-Rotterdam-Milano-Toulouse In Collaboration). *J Am Coll Cardiol*. 2013;61:830-836.
 119. Mack MJ, Brennan JM, Brindis R, et al. Outcomes following transcatheter aortic valve replacement in the United States. *JAMA*. 2013;310:2069-2077.
 120. Wenaweser P, Buellesfeld L, Gerckens U, Grube E. Percutaneous aortic valve replacement for severe aortic regurgitation in degenerated bioprostheses: the first valve in valve procedure using the CoreValve revalving system. *Catheter Cardiovasc Interv*. 2007;70:760-764.
 121. Bapat V, Attia R, Redwood S, et al. Use of transcatheter heart valves for a valve-in-valve implantation in patients with degenerated aortic bioprostheses: technical considerations and results. *J Thorac Cardiovasc Surg*. 2012;144:1372-1379; discussion 1379-1380.
 122. Dvir D, Webb J, Brecker S, et al. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. *Circulation*. 2012;126:2335-2344.
 123. Sarkar K, Ussia GP, Tamburino C. Transcatheter aortic valve implantation for severe aortic regurgitation in a stentless bioprosthetic valve with the Core Valve revalving system—technical tips and role of the Accutrak system. *Catheter Cardiovasc Interv*. 2011;78:485-490.
 124. Seiffert M, Conradi L, Baldus S, et al. Transcatheter mitral valve-in-valve implantation in patients with degenerated bioprostheses. *JACC Cardiovasc Interv*. 2012;5:341-349.
 125. Webb JG, Wood DA, Ye J, et al. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. *Circulation*. 2010;121:1848-1857.
 126. Cerillo AG, Chiaramonti F, Murzi M, et al. Transcatheter valve in valve implantation for failed mitral and tricuspid bioprosthesis. *Catheter Cardiovasc Interv*. 2011;78:987-995.
 127. Seiffert M, Franzen O, Conradi L, et al. Series of transcatheter valve-in-valve implantations in high-risk patients with degenerated bioprostheses in aortic and mitral position. *Catheter Cardiovasc Interv*. 2010;76:608-615.
 128. Simonato M, Whisenant B, Ribeiro HB, et al. Transcatheter mitral valve replacement after surgical repair or replacement: comprehensive midterm evaluation of valve-in-valve and valve-in-ring implantation from the VIVID Registry. *Circulation*. 2021;143:104-116.
 129. Dvir D, Webb JG, Bleiziffer S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA*. 2014;312:162-170.
 130. Webb JG, Mack MJ, White JM, et al. Transcatheter aortic valve implantation within degenerated aortic surgical bioprostheses: PARTNER 2 valve-in-valve registry. *J Am Coll Cardiol*. 2017;69:2253-2262.
 131. Zegdi R, Lecuyer L, Achouh P, et al. Increased radial force improves stent deployment in tricuspid but not in bicuspid stenotic native aortic valves. *Ann Thorac Surg*. 2010;89:768-772.
 132. Svensson LG. Aortic valve stenosis and regurgitation: an overview of management. *J Cardiovasc Surg (Torino)*. 2008;49:297-303.
 133. Chiam PT, Chao VT, Tan SY, et al. Percutaneous transcatheter heart valve implantation in a bicuspid aortic valve. *JACC Cardiovasc Interv*. 2010;3:559-561.
 134. Hayashida K, Bouvier E, Lefèvre T, et al. Transcatheter aortic valve implantation for patients with severe bicuspid aortic valve stenosis. *Circ Cardiovasc Interv*. 2013;6:284-291.
 135. Himbert D, Pontnau F, Messika-Zeitoun D, et al. Feasibility and outcomes of transcatheter aortic valve implantation in high-risk patients with stenotic bicuspid aortic valves. *Am J Cardiol*. 2012;110:877-883.

136. Kochman J, Huczek Z, Koltowski L, Michalak M. Transcatheter implantation of an aortic valve prosthesis in a female patient with severe bicuspid aortic stenosis. *Eur Heart J*. 2012;33:112.
137. Wijesinghe N, Ye J, Rodés-Cabau J, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve stenosis. *JACC Cardiovasc Interv*. 2010;3:1122-1125.
138. Yousef A, Simard T, Poudjabbar A, et al. Performance of transcatheter aortic valve implantation in patients with bicuspid aortic valve: systematic review. *Int J Cardiol*. 2014;176:562-564.
139. Mylotte D. Transcatheter aortic valve replacement in bicuspid aortic valve disease. American College of Cardiology (ACC)/i2 Scientific Session. 2014.
140. Makkar RR, Yoon SH, Chakravarty T, et al. Association between transcatheter aortic valve replacement for bicuspid vs tricuspid aortic stenosis and mortality or stroke among patients at low surgical risk. *JAMA*. 2021;326:1034-1044.
141. Testa L, Latib A, Rossi ML, et al. CoreValve implantation for severe aortic regurgitation: a multicentre registry. *EuroIntervention*. 2014;10:739-745.
142. Seiffert M, Diemert P, Koschky D, et al. Transapical implantation of a second-generation transcatheter heart valve in patients with noncalcified aortic regurgitation. *JACC Cardiovasc Interv*. 2013;6:590-597.
143. Généreux P, Head SJ, Van Mieghem NM, et al. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. *J Am Coll Cardiol*. 2012;59:2317-2326.
144. Eggebrecht H, Schermund A, Voigtländer T, Kahlert P, Erbel R, Mehta RH. Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients. *EuroIntervention*. 2012;8:129-138.
145. Hahn RT, Pibarot P, Webb J, Rodés-Cabau J, et al. Outcomes with post-dilatation following transcatheter aortic valve replacement: the PARTNER I trial (placement of aortic transcatheter valve). *JACC Cardiovasc Interv*. 2014;7:781-789.
146. Nombela-Franco L, Rodés-Cabau J, DeLarochelière R, et al. Predictive factors, efficacy, and safety of balloon post-dilatation after transcatheter aortic valve implantation with a balloon-expandable valve. *JACC Cardiovasc Interv*. 2012;5:499-512.
147. Athappan G, Gajulapalli RD, Sengodan P, et al. Influence of transcatheter aortic valve replacement strategy and valve design on stroke after transcatheter aortic valve replacement: a meta-analysis and systematic review of literature. *J Am Coll Cardiol*. 2014;63:2101-2110.
148. Kahlert P, Knipp SC, Schlamann M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation*. 2010;121:870-878.
149. Van Mieghem NM, Schipper ME, Ladich E, et al. Histopathology of embolic debris captured during transcatheter aortic valve replacement. *Circulation*. 2013;127:2194-2201.
150. Kapadia SR, Kodali S, Makkar R, et al. Protection against cerebral embolism during transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2017;69:367-377.
151. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. *J Am Coll Cardiol*. 2013;61:1585-1595.
152. Généreux P, Head SJ, Hahn R, et al. Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel? A comprehensive review of the literature. *J Am Coll Cardiol*. 2013;61:1125-1136.
153. Hahn RT, Pibarot P, Stewart WJ, et al. Comparison of transcatheter and surgical aortic valve replacement in severe aortic stenosis: a longitudinal study of echocardiography parameters in cohort A of the PARTNER trial (placement of aortic transcatheter valves). *J Am Coll Cardiol*. 2013;61:2514-2521.
154. Kodali S, Pibarot P, Douglas PS, et al. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards SAPIEN valve in the PARTNER trial: characterizing patients and impact on outcomes. *Eur Heart J*. 2015;36:449-456.
155. Lerakis S, Hayek SS, Douglas PS. Paravalvular aortic leak after transcatheter aortic valve replacement: current knowledge. *Circulation*. 2013;127:397-407.
156. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation*. 2011;123:299-308.
157. Nombela-Franco L, Ruel M, Radhakrishnan S, et al. Comparison of hemodynamic performance of self-expandable CoreValve versus balloon-expandable Edwards SAPIEN aortic valves inserted by catheter for aortic stenosis. *Am J Cardiol*. 2013;111:1026-1033.
158. Watanabe Y, Hayashida K, Yamamoto M, et al. Transfemoral aortic valve implantation in patients with an annulus dimension suitable for either the Edwards valve or the CoreValve. *Am J Cardiol*. 2013;112:707-713.
159. Gripari P, Ewe SH, Fusini L, et al. Intraoperative 2D and 3D transoesophageal echocardiographic predictors of aortic regurgitation after transcatheter aortic valve implantation. *Heart*. 2012;98:1229-1236.
160. John D, Buellesfeld L, Yuecel S, Mueller R, et al. Correlation of device landing zone calcification and acute procedural success in patients undergoing transcatheter aortic valve implantations with the self-expanding CoreValve prosthesis. *JACC Cardiovasc Interv*. 2010;3:233-243.
161. Marwan M, Achenbach S, Ensminger SM, et al. CT predictors of post-procedural aortic regurgitation in patients referred for transcatheter aortic valve implantation: an analysis of 105 patients. *Int J Cardiovasc Imaging*. 2013;29:1191-1198.
162. Détaint D, Lepage L, Himbert D, et al. Determinants of significant paravalvular regurgitation after transcatheter aortic valve: implantation impact of device and annulus incongruence. *JACC Cardiovasc Interv*. 2009;2:821-827.
163. Schultz C, Rossi A, Van Mieghem N, et al. Aortic annulus dimensions and leaflet calcification from contrast MSCT predict the need for balloon post-dilatation after TAVI with the Medtronic CoreValve prosthesis. *EuroIntervention*. 2011;7:564-572.
164. Daneault B, Koss E, Hahn RT, et al. Efficacy and safety of postdilatation to reduce paravalvular regurgitation during balloon-expandable transcatheter aortic valve replacement. *Circ Cardiovasc Interv*. 2013;6:85-91.
165. Makkar RR, Jilaihawi H, Chakravarty T, et al. Determinants and outcomes of acute transcatheter valve-in-valve therapy or embolization: a study of multiple valve implants in the U.S. PARTNER trial (Placement of Aortic Transcatheter Valve Trial Edwards SAPIEN Transcatheter Heart Valve). *J Am Coll Cardiol*. 2013;62:418-430.
166. Aktug Ö, Dohmen G, Brehmer K, et al. Incidence and predictors of left bundle branch block after transcatheter aortic valve implantation. *Int J Cardiol*. 2012;160:26-30.
167. Piazza N, Onuma Y, Jessurun E, Kint PP, et al. Early and persistent intraventricular conduction abnormalities and requirements for pacemaking after percutaneous replacement of the aortic valve. *JACC Cardiovasc Interv*. 2008;1:310-316.
168. Erkapic D, De Rosa S, Kelava A, Lehmann R, Fichtlscherer S, Hohnloser SH. Risk for permanent pacemaker after transcatheter aortic valve implantation: a comprehensive analysis of the literature. *J Cardiovasc Electrophysiol*. 2012;23:391-397.
169. Khatri PJ, Webb JG, Rodés-Cabau J, et al. Adverse effects associated with transcatheter aortic valve implantation: a meta-analysis of contemporary studies. *Ann Intern Med*. 2013;158:35-46.
170. Urena M, Webb JG, Tamburino C, et al. Permanent pacemaker implantation after transcatheter aortic valve implantation: impact on late clinical outcomes and left ventricular function. *Circulation*. 2014;129:1233-1243.
171. Amat-Santos IJ, Rodés-Cabau J, Urena M, et al. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2012;59:178-188.
172. Genereux P, Kodali S, Leon MB, et al. Clinical outcomes using a new crossover balloon occlusion technique for percutaneous closure after transfemoral aortic valve implantation. *JACC Cardiovasc Interv*. 2011;4:861-867.
173. Hayashida K, Lefèvre T, Chevalier B, et al. True percutaneous approach for transfemoral aortic valve implantation using the Prostar XL device: impact of learning curve on vascular complications. *JACC Cardiovasc Interv*. 2012;5:207-214.
174. Storteky S, Wenaweser P, Diehm N, et al. Percutaneous management of vascular complications in patients undergoing transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. 2012;5:515-524.
175. Ribeiro HB, Webb JG, Makkar RR, et al. Predictive factors, management, and clinical outcomes of coronary obstruction following transcatheter aortic valve implantation: insights from a large multicenter registry. *J Am Coll Cardiol*. 2013;62:1552-1562.
176. Dvir D, Leipsic J, Blanke P, et al. Coronary obstruction in transcatheter aortic valve-in-valve implantation: preprocedural evaluation, device selection, protection, and treatment. *Circ Cardiovasc Interv*. 2015;8(1):e002079.
177. Khan JM, Greenbaum AB, Babaliaros VC, et al. BASILICA Trial: one-year outcomes of transcatheter electrosurgical leaflet laceration to prevent TAVR coronary obstruction. *Circ Cardiovasc Interv*. 2021;14:e010238.
178. Barbanti M, Yang T-H, Rodés-Cabau J, et al. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. *Circulation*. 2013;128:244-253.
179. Cota L, Stabile E, Agrusta M, et al. Bioprostheses "thrombosis" after transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2013;61:789-791.
180. Latib A, Messika-Zeitoun D, Maisano F, et al. Reversible Edwards SAPIEN XT dysfunction due to prosthesis thrombosis presenting as early structural deterioration. *J Am Coll Cardiol*. 2013;61:787-799.
181. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015-2024.
182. Makkar RR, Blanke P, Leipsic J, et al. Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves: PARTNER 3 cardiac computed tomography substudy. *J Am Coll Cardiol*. 2020;75:3003-3015.
183. Blanke P, Leipsic JA, Popma JJ, et al. Bioprosthetic aortic valve leaflet thickening in the Evolut low risk sub-study. *J Am Coll Cardiol*. 2020;75:2430-2442.
184. Montalescot G, Redheuil A, Vincent F, et al. Apixaban and valve thrombosis after transcatheter aortic valve implantation: the ATLANTIS 4D-CT randomized clinical trial substudy. *JACC Cardiovasc Interv*. 2022;15(18):1794-1804.
185. Urena M, Doyle D, Rodés-Cabau J, Dumont E. Initial experience of transcatheter aortic valve replacement with the St Jude Medical Portico valve inserted through the transapical approach. *J Thorac Cardiovasc Surg*. 2013;146:e24-e27.
186. Makkar RR, Cheng W, Waksman R, et al. Self-expanding intra-annular versus commercially available transcatheter heart valves in high and extreme risk patients with severe aortic stenosis (PORTICO IDE): a randomised, controlled, non-inferiority trial. *Lancet*. 2020;396:669-683.

187. Kempfert J, Treede H, Rastan AJ, et al. Transapical aortic valve implantation using a new self-expandable bioprosthesis (ACURATE TA™): 6-month outcomes. *Eur J Cardiothorac Surg*. 2013;43:52-56; discussion 57.
188. Möllmann H, Diemert P, Grube E, Baldus S, Kempfert J, Abizaid A. Symetis ACURATE TF™ aortic bioprosthesis. *EuroIntervention*. 2013;9(suppl):S107-S110.
189. Lanz J, Kim WK, Walther T, et al. Safety and efficacy of a self-expanding versus a balloon-expandable bioprosthesis for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: a randomised non-inferiority trial. *Lancet*. 2019;394:1619-1628.
190. Tamburino C, Bleiziffer S, Thiele H, et al. Comparison of self-expanding bioprostheses for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: SCOPE 2 randomized clinical trial. *Circulation*. 2020;142:2431-2442.
191. Silaschi M, Treede H, Rastan AJ, et al. The JUPITER registry: 1-year results of transapical aortic valve implantation using a second-generation transcatheter heart valve in patients with aortic stenosis. *Eur J Cardiothorac Surg*. 2016;50:874-881.
192. Treede H. An early feasibility study to assess the safety and effectiveness of the transfemoral JenaValve pericardial TAVR system in the treatment of patients with symptomatic severe aortic stenosis. *Transcatheter Cardiovascular Therapeutics*. 2018.
193. Thourani V. 30-day outcomes from an EFS to assess the safety and effectiveness of a novel TF TAVR system for the treatment of patients with symptomatic severe AR. *Transcatheter Valve Therapeutics*. 2019.



30

Transcatheter Mitral Valve Intervention

SAIF ANWARUDDIN AND HOWARD C. HERRMANN

INTRODUCTION: NORMAL MITRAL VALVE ANATOMY, 554

MITRAL VALVE DISEASE STATES, 554

MITRAL STENOSIS, 554

Causes of Mitral Stenosis, 554

Pathology of Rheumatic Mitral Stenosis, 555

Pathophysiology of Rheumatic Mitral Stenosis, 555

Clinical Presentation of Mitral Stenosis, 555

Management of Mitral Stenosis, 557

Special Consideration: Pregnancy, 563

MITRAL REGURGITATION, 563

PATHOPHYSIOLOGY, 563

Rationale for Transcatheter Therapy, 564

Leaflet Repair with the MitraClip Device, 564

Indirect Annuloplasty, 565

Direct Annuloplasty and Left Ventricular

Remodeling Techniques, 566

Transcatheter Mitral Valve Replacement, 567

CONCLUSIONS, 570

INTRODUCTION: NORMAL MITRAL VALVE ANATOMY

To appreciate the complexity of the mitral valve is to understand its intricate anatomic and physiologic properties. The mitral valve can be divided into several components, each one important in maintaining proper valve functionality. The mitral valve consists of two leaflets, a posterior leaflet with three distinct scallops and a corresponding, but much larger, anterior leaflet. The two mitral valve leaflets are continuous with each other and maintain a connection at the commissures. The anterior leaflet is continuous with the ascending aorta and the membranous ventricular septum. The leaflets anchor to the myocardium by way of two papillary muscles, the anterolateral and posteromedial. The anterolateral papillary muscle is usually the larger of the two structures. The attachment between the papillary muscle and the valve leaflets occurs by way of chordae tendineae.

With systolic contraction of the left ventricular (LV) cavity, the resultant traction of the papillary muscles leads to valve closure by transmission of the force through the chordae. The chordae tendineae insert on the underside of the leaflet tissue. Blood in the ventricular chamber passes through interchordal spaces on its route from the left atrium.

The two mitral valve leaflets attach to the base of the left atrium to a thin ovoid-shaped membrane—the mitral valve annulus. The annulus itself is a nonplanar saddle-shaped structure that functions to influence valve competency.¹ In close proximity to the anterior portion of the mitral valve annulus are two fibrous trigones, which are separated by the fibrous intertrigonal region. The posterior portion of the annulus is not surrounded by any fibrous tissue, however, and serves to separate the ventricular tissue from the atria.

The coronary sinus generally lies close to the posterior side of the mitral valve annulus. This anatomic relationship allows for the use of percutaneous annuloplasty techniques. There is variability in the relationship between the annulus and the coronary sinus and is likely influenced by the size of the left atrium and other factors. For the purpose of percutaneous interventions on the mitral valve apparatus, it is important to consider the relationship

between the coronary sinus and the course of the left circumflex coronary artery. Cardiac computed tomography has been used to demonstrate that the left circumflex artery crosses between the mitral annulus and the coronary sinus in the vast majority of patients with significant variability in the location of crossover.²

Disease of the mitral valve can be primarily valvular or secondary to other processes, notably those affecting the myocardium. The standard of care for treatment of patients with mitral valve disease has been primarily surgical. Several percutaneous approaches to treating mitral valve disease have emerged and continue to evolve as possible alternatives to surgical treatment, particularly in patients not considered appropriate surgical candidates. As such, an appreciation for the complexity of mitral valve anatomy is necessary to understand how and why percutaneous approaches work in treatment of patients with mitral valve disease.

MITRAL VALVE DISEASE STATES

MITRAL STENOSIS

Causes of Mitral Stenosis

The primary disturbance in mitral stenosis (MS) is an obstruction to the inflow of blood from the left atrium into the left ventricle during diastole. Worldwide, the primary cause of MS is rheumatic heart disease. Rheumatic changes can affect the mitral valve itself and the subvalvular apparatus as well. Less common causes of MS include congenital abnormalities such as cor triatriatum and parachute mitral valve and noncongenital causes such as left atrial (LA) myxoma, endocarditis, carcinoid, mucopolysaccharidosis, rheumatoid arthritis, and systemic lupus erythematosus, among others.

Lutembacher syndrome denotes the presence of a secondary atrial septal defect and rheumatic MS. In the older adult population, severe mitral annular calcifications can lead to varying degrees of MS and mitral regurgitation (MR). For the remainder of the discussion on MS and its treatment by percutaneous balloon mitral valvuloplasty, we will focus only on rheumatic MS.

Pathology of Rheumatic Mitral Stenosis

As mentioned, the most common cause of MS worldwide is rheumatic heart disease. In patients with rheumatic MS, as many as half of patients are not aware of a history of rheumatic fever. After an episode of acute rheumatic fever, it may take several years before the development of MS and many more years until the development of symptoms. Progression of disease and development of clinical symptoms correlate with episodes of rheumatic fever.³ Ongoing inflammatory insults affecting the valve may result in eventual clinical manifestations.

The basis for the development of MS after streptococcal infection is believed to be molecular mimicry. The similarity between streptococcal bacterial M protein and human cardiac proteins (myosin and others) is likely the reason for molecular mimicry between the two organisms. Humoral and cellular responses are important in the pathogenesis, and the CD4+ T cell response is the main culprit of the molecular mimicry response affecting cardiac tissue.⁴

In rheumatic MS, there is diffuse fibrous thickening of the mitral valve leaflets with calcific deposits. In addition to fibrous thickening, there is fusion of the leaflet commissures along with shortening and fusion of the subvalvular chordae tendineae. The amount of calcification of the valve leaflets itself is variable. This process is not, however, limited to the valves because it affects the three layers of the heart as well with increased amounts of fibrous tissue.

Pathophysiology of Rheumatic Mitral Stenosis

In addition to the characteristic findings of MS on the valve, these structures can also be affected by concomitant calcification. In combination, these changes result in significant restriction in the opening of the mitral leaflet. As such, there is a severe reduction in size of the mitral valve orifice, leading to a funnel-shaped orifice often described as “fish mouth” in appearance. Also, there can be associated MR caused by leaflet malcoaptation arising from fibrosis and shortening of the subvalvular apparatus, including the chordae.

The end result of these changes on the mitral valve complex is a restriction of blood flow across the mitral valve orifice. The normal mitral valve has an orifice area of between 4 and 6 cm². MS is a slowly progressive disease that worsens over the course of many years. With a reduction in mitral valve orifice area, a higher transvalvular pressure gradient may develop, leading to increased LA pressure. There is then transmission of elevated LA pressure into the pulmonary vasculature, eventually leading to the development of pulmonary venous pressures. Long-standing MS and increased LA pressures can lead to severe and irreversible pulmonary hypertension from elevated LA pressures, pulmonary vascular constriction, and obliterative changes to the vasculature.

With chronically elevated pulmonary arterial pressures in long-standing and untreated MS, patients can develop right ventricular (RV) dilatation and dysfunction over time. With development of severe tricuspid valve regurgitation as a consequence, signs and symptoms of right heart failure can develop. Most patients start to develop symptoms when the mitral valve area (MVA) is between

1.0 and 1.5 cm² in area. It is important to understand that the process can affect other valves and the myocardium, leading to ventricular dysfunction, which can contribute to symptoms.

Clinical Presentation of Mitral Stenosis

Clinical Manifestations

Patients often present with symptoms related to MS several years to decades after their initial bout of rheumatic fever. In developing countries, this may occur sooner because of repeat bouts of rheumatic fever. With development of symptoms, long-term survival is severely compromised.

According to the World Health Organization, reliable statistics on the incidence and prevalence of rheumatic fever are not easily available. However, the annual incidence in developing countries has been reported to vary between 1 to more than 150 per 100,000 school-age children. The prevalence of rheumatic heart disease varies from between 0.5 per 1000 school-age children in developed countries to more than 70 per 1000 school-age children in other developing countries. It is reported that rates vary even within developing countries, and hospital admissions for rheumatic heart disease vary between 12% and 65%.⁵

The diagnosis of rheumatic fever is made based on the Jones criteria, first published by Dr. T. Duckett Jones in 1944 and since revised. The presence of two major or one major and two minor criteria must be met. The major criteria include carditis, polyarthritis, erythema marginatum, chorea, and subcutaneous nodules. The minor criteria include fever, arthralgias, elevated erythrocyte sedimentation rate, elevated C-reactive protein, and prolonged PR interval. These findings are used in the context of a documented Group A β -hemolytic streptococcal throat infection.

Although the progression in the rate of mitral valve stenosis is variable, it is estimated to be about a 0.1-cm² reduction in valve area per year.⁶ The onset of clinical manifestations is also variable. The primary symptom in mitral valve stenosis is exertional dyspnea secondary to elevated LA pressures and elevated pulmonary venous and arterial pressures. This is often accompanied by orthopnea, coughing, and wheezing. Even when MS is less advanced, coexistent conditions such as anemia, pregnancy, infection, atrial fibrillation, exertion, or fever can precipitate symptoms by decreasing diastolic filling time and increasing blood flow across the stenotic mitral orifice.

With progression of disease, patients can experience pulmonary edema, atrial fibrillation, pulmonary hemorrhage from rupture of dilated bronchial veins, and chest pain. Other less common symptoms include systemic embolization, clinical signs and symptoms of right heart failure, and hoarseness caused by compression of the left recurrent laryngeal nerve by dilated pulmonary artery (PA), enlarged lymph nodes, or an enlarged left atrium (Ortner's syndrome).

Clinical Assessment: History and Physical Examination

Often, obtaining a history in a patient with rheumatic MS does not reliably reveal a prior history of rheumatic fever.

Furthermore, given the slow progression of the disease, many patients report being asymptomatic and deny frank exertional dyspnea. It is important to note that given the slow progression, patients reduce their level of activity to remain without symptoms.

Patients with severe MS demonstrate purple and pink patches on the cheeks termed “mitral facies.”⁷ It is important to remember that in those with severe MS, LA function may be normal, and LA filling pressures may be low or normal. As such, palpation of the left ventricle will likely reveal a normal apical impulse. With palpation, a left parasternal RV heave can sometimes be appreciated in the setting of pulmonary hypertension. Jugular venous pressure can be elevated in the setting of RV dysfunction.

Auscultation of a patient with severe MS will reveal several characteristics about the mitral valve itself. The characteristic findings on auscultation are that of a loud S1, an opening snap (OS), and a mid-diastolic murmur, described as a rumble. The OS follows A2 and can be best heard at the left lower sternal border. The pliability of anterior mitral leaflet is the source of the sound for the OS. The OS usually follows the A2 sound by 0.04 to 0.12 seconds. During exhalation, it is possible to differentiate the physiologic splitting of the second heart sound from the OS because the two sounds are that of the S2 followed by the OS. The duration of time between the A2 and the OS is also a marker of severity of disease. Specifically, increased pressure gradient or elevated LA pressure leads to faster opening of the mitral valve in diastole. As such, the time duration between A2 and OS is markedly shorter in the setting of higher LA pressure and severity of MS. Maneuvers that decrease venous blood return serve to increase the A2 to OS interval.

The diastolic murmur of MS is best appreciated with the patient in the left lateral decubitus position and is often described as a low-pitch rumble at the apex. The duration of the murmur is a marker for severity of disease because it is driven by the gradient across the left atrium and ventricle. Maneuvers such as exhalation can accentuate the MS murmur, and the Valsalva maneuver can serve to decrease the intensity of the diastolic murmur because of a reduction in flow across the mitral valve.

Clinical Assessment with Diagnostic Tools

The diagnostic workup of the patient with MS relies heavily on the echocardiographic findings. The electrocardiogram (ECG) and chest x-ray examination are at times helpful, but the diagnosis squarely rests on the results of noninvasive imaging. The ECG often reveals findings consistent with LA enlargement, and chest radiography can demonstrate LA enlargement as well as enlargement of the pulmonary vasculature and pulmonary edema on occasion.

Echocardiography

Transthoracic (TTE) or transesophageal (TEE) echocardiography can be used to diagnose and to determine the severity of MS (Figure 30.1). TTE can be helpful in the assessment of the morphology, mobility, and function of the mitral valve itself. The characteristic thickening and doming, or “hockey stick” appearance, of the anterior mitral leaflet can be appreciated in the parasternal long-axis view on TTE. There is a reduction in leaflet mobility noted, and TTE can also be used to quantify the degree of MR, if any. In addition, TTE can be useful in the assessment of the subvalvular apparatus, the degree of calcification of the valve leaflets, commissures and the subvalvular apparatus, pulmonary arterial pressures, and concomitant valvular disease.

Determining the morphology of the mitral valve and the subvalvular apparatus is important in preprocedural planning for balloon mitral valvuloplasty. The suitability of a valve for balloon mitral valvuloplasty can be determined using the Wilkins criteria, which scores four features of the valve, including leaflet mobility, leaflet thickening, leaflet calcification, subvalvular calcification, and thickening. Each feature is assigned a score from 1 to 4, and higher valve scores (maximum, 16) predict unfavorable outcomes with mitral valvuloplasty.⁸

Assessment of mitral valve gradients is best performed with TTE in the apical four-chamber view with the Doppler beam parallel to the mitral jet to obtain the most accurate gradients. Assessment of MVA with TTE can be performed with planimetry, continuity equation, or with pressure half-time (PHT) measurements. Planimetry of the mitral valve orifice is performed using the parasternal short-axis

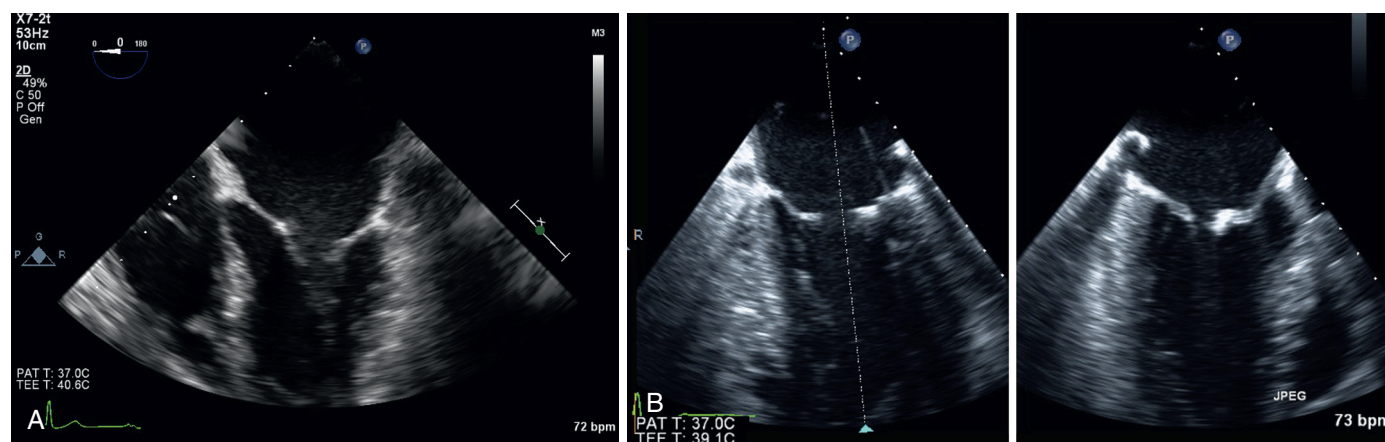


FIGURE 30.1 **A**, Transesophageal echocardiogram (TEE) demonstrating rheumatic mitral stenosis. Note the leaflet thickening and restricted opening of the valve leaflets. **B**, TEE of mitral valve opening and closing in a patient with rheumatic mitral stenosis.

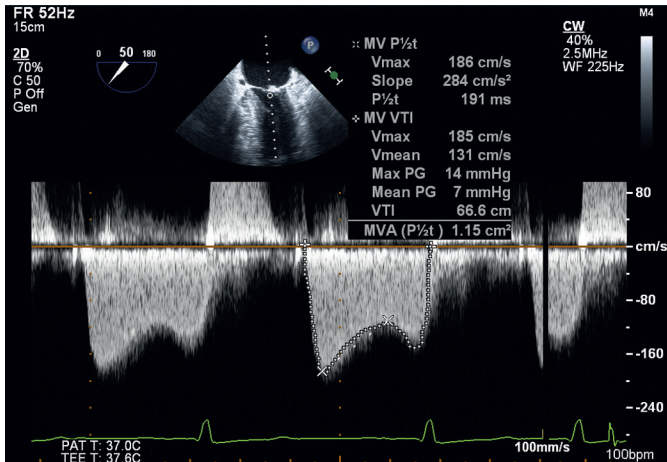


FIGURE 30.2 Calculating mitral valve area in a patient with rheumatic mitral stenosis using the pressure half-time formula.

view, and it is important to start imaging at the apex and move upward to identify the smallest mitral valve orifice for measurement. This method can at times lead to overestimation of the MVA if the imaging plane is proximal to the true orifice or caused by irregularities in the orifice itself.

The PHT is a flow-dependent method that estimates MVA based on the time needed for the peak gradient across the valve to fall by half (Figure 30.2). The slope derived from this decrease is related to the degree of stenosis. With more severe stenosis, there is a larger gradient and a smaller mitral orifice, which result in a longer time for pressure decline and a longer PHT. With PHT, one can calculate MVA as follows:

$$\text{MVA} = 220 / \text{PHT}$$

When there is an alteration in the LA or LV pressures, the PHT measurement can be unreliable. In the setting of LV dysfunction with increased left ventricular end-diastolic pressure (LVEDP), the PHT will be shortened, thus overestimating the MVA. In patients with severe aortic regurgitation, the increase in LVEDP can also lead to shortening of the PHT and an overestimation of the MVA.

Transesophageal echocardiography can be used to further assess the morphology of the mitral valve and the subvalvular apparatus. Before catheter-based intervention, TEE can be used to assess for LA or LA appendage thrombus in patients with atrial fibrillation. TEE can also be used to help guide catheter-based interventions, including safely crossing the atrial septum into the left atrium, and to assess mitral valve morphology after balloon valvuloplasty.

Exercise stress echocardiography can also be used in the assessment of mitral valve stenosis severity. It can be used to evaluate exercise tolerance in patients with MS who are otherwise asymptomatic or to assess severity of otherwise mild MS at rest in patients with clear symptoms. Exercise testing can also be performed with a PA catheter. Significant increases in pulmonary artery systolic pressures (PASP) or mean mitral valve gradients can help identify patients who would benefit from mitral valvuloplasty.⁹

Cardiac Catheterization and Angiography

Although echocardiography remains the mainstay of diagnosis, cardiac catheterization is not only a confirmatory diagnostic modality because it serves to resolve discrepancies between clinical and noninvasive imaging findings, assess for coronary atherosclerosis as cause of symptoms, or before mitral valve surgery. It also serves to help determine the role of MS in patients with concomitant lung disease.

Assessment of mitral valve gradients can be accomplished using an LV pigtail catheter and a PA catheter with pulmonary capillary wedge pressure (PCWP) measurements as a surrogate for LA pressure. The PCWP tends to overestimate the gradients across the mitral valve. The use of the PCWP may be unreliable in patients with pulmonary veno-occlusive disease. Direct measurement of the LA pressure can also be accomplished by crossing the atrial septum under fluoroscopic or echocardiographic guidance. Accurate gradients can be calculated using direct LA and LV measurements (Figure 30.3).

The MVA can be calculated using the Gorlin formula. Cardiac output can be calculated using right heart catheterization with the thermodilution, or Fick measurements. In patients with low output or concomitant regurgitant valvular lesions, Fick measurements of cardiac output may be more accurate. The Gorlin formula is as follows:

$$\text{MVA (cm}^2\text{)} = [\text{SV/DFP}] / [\text{K} * (\text{sq rt mean MV gradient})]$$

in which SV is stroke volume; DFP is diastolic filling period (in seconds); and K is a constant, which is 37.7 for the MV. The Hakki formula can also be used to calculate MVA as follows:

$$\text{MVA (cm}^2\text{)} = \text{CO} / (\text{sq rt mean MV gradient})$$

In patients with MS and atrial fibrillation, the mean mitral valve gradient should be averaged over 10 beats. Measurements of gradients and calculations of valve area are highly dependent on flow and heart rate. Elevated gradients are noted in conditions that cause tachycardia or decrease the diastolic filling period.

Management of Mitral Stenosis

Medical Therapy for Mitral Stenosis

Antibiotic therapy is the mainstay of therapy in patients with rheumatic fever and prophylaxis in certain populations to reduce the risk of recurrence. In patients with rheumatic heart disease, medical therapy is aimed at improving symptoms and reducing conditions that lead to tachycardia. Diuretics and careful restriction of sodium intake can be used for treatment of pulmonary edema and pulmonary venous congestion in symptomatic patients. Treatment of anemia, dehydration, concomitant thyroid disease, fever, infection, and other conditions can help to alleviate symptoms in patients with MS.

The use of beta-blockers and calcium channel blockers can be used to lower the heart rate and increase the diastolic filling time. In the setting of atrial fibrillation, which occurs commonly in patients with MS, the goal of treatment should be rate control with beta-blockers, calcium channel blockers, or digoxin or consideration of electrical

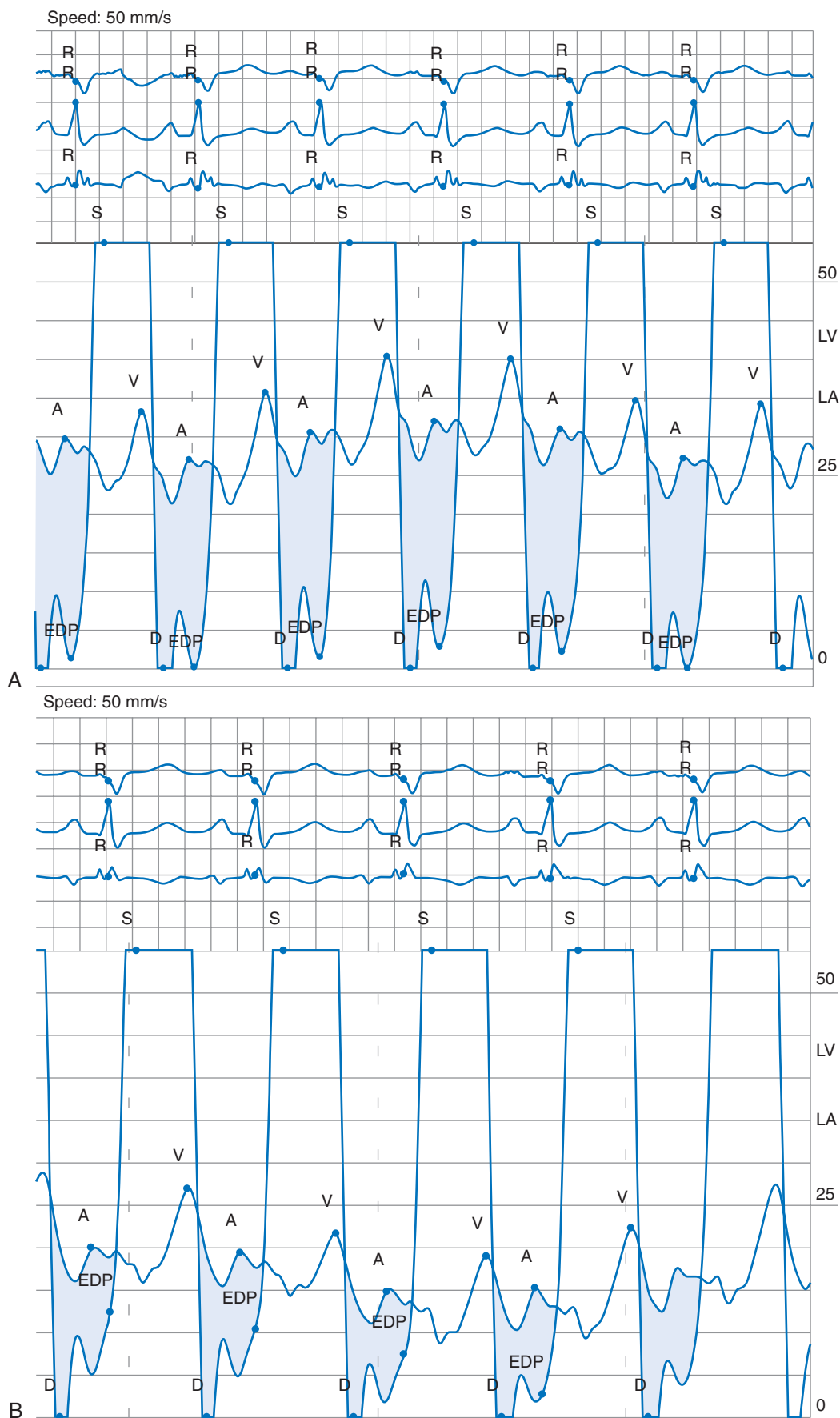


FIGURE 30.3 **A**, Direct left atrial (LA) and left ventricular (LV) pressure tracings demonstrating a gradient of 23 mm Hg from rheumatic mitral stenosis. **B**, Direct left atrial and left ventricular pressure tracings after a single inflation of a balloon in a percutaneous balloon mitral valvuloplasty on the same patient in **A**. The mean gradient is between 11 to 12 mm Hg. EDP, End-diastolic pressure.

cardioversion after exclusion of LA thrombus by TEE. When atrial fibrillation with rapid ventricular rates is not well tolerated hemodynamically, emergent cardioversion may be necessary in the absence of an assessment for LA thrombus. Anticoagulation should be initiated in any patient with MS and atrial fibrillation, assuming there are no other contraindications. Given the risk of systemic embolization, anticoagulation has been suggested in patients with MS even without evidence of atrial fibrillation. Per the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, anticoagulation is a Class I indication in patients with atrial fibrillation, prior embolic event, and with evidence for LA thrombus. Anticoagulation is a Class IIb recommendation in patients with severe MS and dilated left atrium or with evidence of spontaneous echo contrast.¹⁰ After mitral valve intervention, atrial fibrillation can persist and needs to be managed appropriately.

Catheter-Based Treatment of Mitral Stenosis

Indications for Catheter-Based Treatment

Percutaneous mitral balloon valvuloplasty (PMBV) as a treatment for patients with rheumatic MS was first described separately both by Inoue and Lock in the mid-1980s. Before this, surgery was the only treatment modality. PMBV is indicated in patients with symptomatic MS who have at least moderate to severe MS, favorable valve morphology for PMBV with the absence of LA thrombus, or moderate to severe MR. In patients with moderate to severe MS without symptoms and favorable mitral valve morphology, PMBV can be used in treating patients with pulmonary hypertension (PASP at rest ≥ 50 mm Hg or >60 mm Hg with exercise), assuming absence of LA thrombus or moderate to severe MR. In patients with rheumatic MS with calcified nonpliable valves and who are at high risk or unsuitable for open surgery, PMBV is also a reasonable alternative in symptomatic patients with moderate to severe MS.

Per the ACC/AHA Updated Valve Guidelines, PMBV can be considered in an asymptomatic patient with moderate to severe MS and new-onset atrial fibrillation after excluding LA thrombus or moderate to severe MR (Class IIb). In patients with symptoms and mild MS (MVA >1.5 cm²), PMBV can be considered if there is evidence of significant MS on exercise (Class IIb).¹⁰

The proposed mechanism of benefit for patients from PMBV is separation of the fused commissures, which acts to relieve the physical obstruction by reducing the gradient and increasing the MVA.

Patient Selection

Central to successful outcomes with any percutaneous or surgical procedure is optimal patient selection. In the case of MS, optimal mitral valve and subvalvular morphology is very important in helping to ensure optimal outcomes with the PMBV procedure. The previously mentioned Wilkins echo score is a widely used assessment tool to determine the suitability of the mitral valve for PMBV. Leaflet mobility, leaflet calcification, leaflet thickening, and subvalvular thickening and calcification are individually graded on a scale of 1 to 4. Typically unfavorable outcomes are predicted with scores greater than 8.⁸

It should be noted that careful noninvasive assessment of the subvalvular apparatus is also an important procedural consideration. Evidence of subvalvular apparatus deformity on echocardiography or absence of a c-wave on a LA pressure waveform can suggest severe deformity. Severe subvalvular deformity can potentially alter post-PMBV results.¹¹

Absolute contraindications to PMBV include the presence of LA thrombus or moderate to severe MR. In the presence of LA thrombus, anticoagulation should be prescribed for 3 months, and PMBV should be considered after resolution of thrombus.

Procedure

The transvenous antegrade transseptal route is most commonly used to gain access to the left atrium to perform PMBV. Two main percutaneous techniques have been described and widely used. The Inoue technique was first used in 1982 and described in 1984.¹² The Inoue technique uses a special balloon with a staged inflation technique. The double-balloon technique is less commonly used, however, and uses two peripheral arterial balloons across the mitral valve with guidewires positioned in the left ventricle.

Transseptal Catheterization

Fundamental to successfully performing PMBV is the ability to gain access to the left atrium safely via the transseptal route. The transseptal procedure was developed and later modified in the late 1950s and 1960s. A careful understanding of septal anatomy is necessary to be able to carry out the procedure (Figure 30.4). Although fluoroscopy is the mainstay for guiding the procedure, adjunct imaging with TEE and intracardiac echocardiography (ICE) has added value to the procedure both in terms of delineating anatomy and for safety.

With the patient in a supine position, the atrial septum spans from the 1 to 7 o'clock positions. The fossa ovalis lies posterior to the aortic root (often best appreciated in the right anterior oblique [RAO] view) and is bordered superiorly by a ridge (limbus). The lie and position of the interatrial septum and the fossa can become distorted in various disease states. In MS, the plane of the septum can become more horizontal, and the septum can become flat.

The transseptal procedure is performed using a Mullins sheath and dilator, which are advanced over a previously placed 0.032-inch J-wire. The wire should be placed into the superior vena cava (SVC) and used to insert and deliver the Mullins sheath and dilator into the SVC. A Brockenbrough needle is a curved needle that can be delivered through the Mullins sheath to allow for transseptal puncture. Additionally, a shield on the proximal end of the needle with an arrow indicates the direction of the curvature of the needle tip. It is imperative to confirm alignment between the arrow tip and the direction of the needle tip.

When the Mullins sheath is positioned in the SVC, the 0.032-inch wire is removed, and the Brockenbrough needle is carefully advanced into the dilator until the tip of the needle lies in the dilator. There should be approximately 2 cm of distance (approximately two finger widths) between the proximal portion of the dilator and the shield of the Brockenbrough needle. At this point, the stylet should be

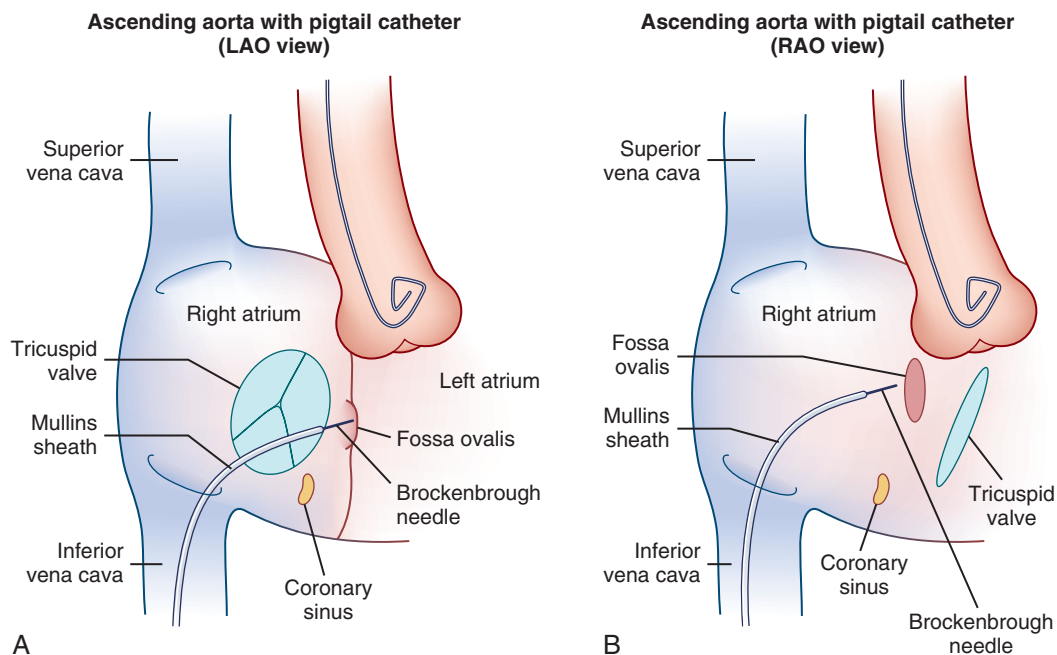


FIGURE 30.4 Illustrations of the anatomy of the transseptal puncture. Left anterior oblique (LAO; **A**) and right anterior oblique (RAO; **B**) projections. (Modified from Earley MJ. How to perform a transseptal puncture. *Heart*. 2009;95(1):85-92.)

removed and the proximal end of the needle should be flushed and attached to a pressure transducer. Many operators obtain 4- or 5-Fr femoral arterial access to place a pigtail catheter in the right coronary sinus to help delineate the position of the aorta.

Before puncture, it is important to verify the needle position and maintain that the sheath and dilator are manipulated as one unit. Then, typically in the PA position, the entire unit is rotated clockwise until the arrow on the Brockenbrough needle is at the 4 o'clock position. The next step is to withdraw the unit into the fossa. On withdrawal, there are three sequential transitions that can be felt with this motion: the first is the SVC-RA junction, next is the ascending aorta, and finally is the limbus of the fossa ovalis. Using a combination of fluoroscopic and echocardiographic imaging to obtain the best views, the operator should confirm accurate positioning of the Mullins sheath-dilator-Brockenbrough needle apparatus.

After the position is confirmed, the entire apparatus should be advanced into the fossa until there is dampening of the right atrial waveform. Some operators inject a small amount of contrast to demonstrate tenting of the septum by the needle. At this point, the apparatus should be advanced, often in the left anterior oblique projection in which the needle should be pointing to the right of the screen, until entry into the left atrium is confirmed with pressure waveform and imaging guidance (Video 30.1). Use of contrast can help confirm position in the left atrium and exclude possibility of aortic or pericardial entry. After entry is confirmed, the entire device is advanced approximately 1 cm using hemodynamic and imaging guidance until the tip of the Mullins dilator is in the left atrium. At this point, the needle is removed, and the 0.032-inch J-wire is reinserted and placed in the left atrium. The sheath and dilator are advanced over the wire, and then

the wire and dilator are removed (Video 30.2). The sheath is flushed carefully, and systemic anticoagulation with heparin is initiated.

Before the use of intracardiac or TEE to guide the transseptal procedure, it was performed using fluoroscopy only. Although single-plane fluoroscopy can be used, the procedure is ideally performed using biplane fluoroscopy to identify the ideal position both in the PA and lateral views. Despite the advantages of biplane over single-plane fluoroscopy, there are several limitations to using only fluoroscopic guidance to perform the procedure. As such, the use of echocardiographic imaging as an adjunct has several distinct advantages over using fluoroscopy alone. Using echocardiographic guidance, confirming proper needle position before puncture can enhance procedural safety. Being able to determine the exact site of puncture can also be helpful in more complex procedures, such as percutaneous mitral valve repair, in which the position of septal entry is important to the procedure itself. For percutaneous mitral valve repair using the MitraClip system, the desired location to enter the septum is high and posterior in the fossa ovalis to allow for device manipulation and delivery (Videos 30.3 and 30.4).

Although TTE has been shown to be of use in transseptal puncture, the use of TEE provides improved visualization of the interatrial septum and surrounding structures. Furthermore, it allows for precise entry across the septum to facilitate more complex procedures. TEE requires an additional operator and requires heavy sedation or general anesthesia to perform the procedure and should be considered as part of procedural planning (Figure 30.5).

Intracardiac echocardiography can also be used to perform imaging of the fossa ovalis and to help guide the transseptal puncture. ICE provides excellent visualization of the septum in addition to being able to guide precise

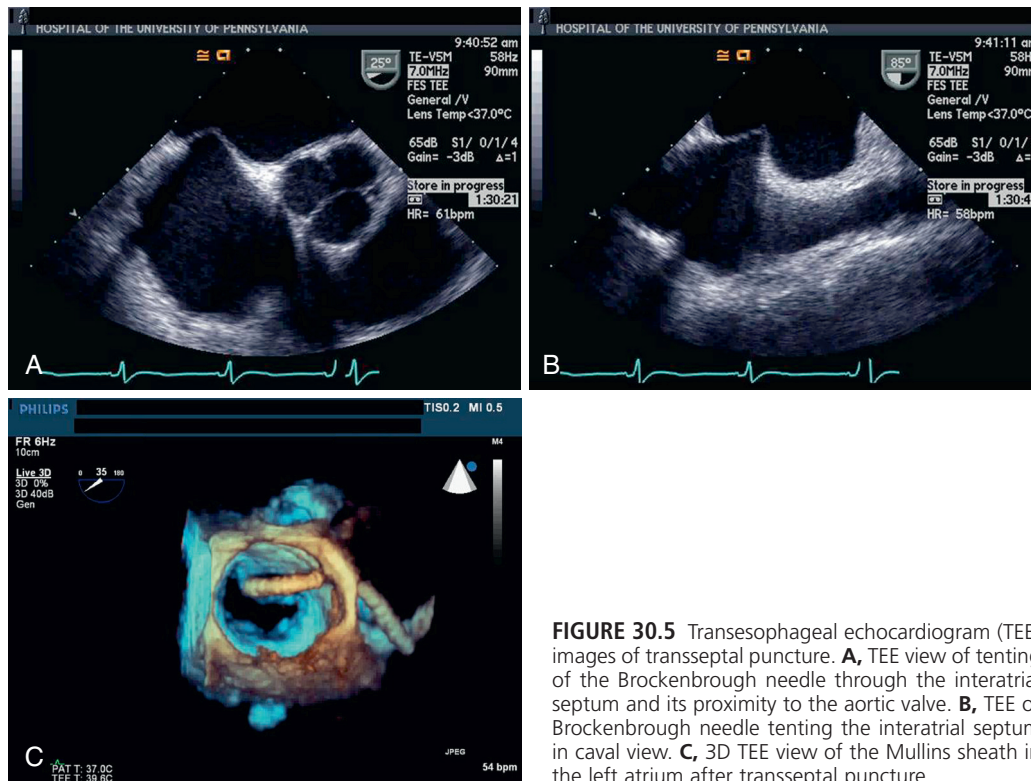


FIGURE 30.5 Transesophageal echocardiogram (TEE) images of transseptal puncture. **A**, TEE view of tenting of the Brockenbrough needle through the interatrial septum and its proximity to the aortic valve. **B**, TEE of Brockenbrough needle tenting the interatrial septum in caval view. **C**, 3D TEE view of the Mullins sheath in the left atrium after transseptal puncture.

entry using direct visualization. In addition to superior imaging TEE, there is no need for general anesthesia, heavy sedation, or an additional operator (Figure 30.6) as in TEE. The ICE catheter requires 8- or 9-Fr contralateral venous access for delivery.

Transseptal puncture can be performed safely and effectively using meticulous technique and adjunctive imaging as a guide. With the use of echocardiographic imaging, hemodynamics, and fluoroscopy, transseptal puncture and catheterization can guide diagnostic procedures and complex therapeutic procedures while minimizing the risk of procedural complications. The decision as to which adjunct imaging modality to use will be heavily influenced by user preference and, ultimately, the planned procedure following transseptal puncture (see the Procedural Imaging section).

Inoue Technique

This Inoue balloon is a self-positioning latex balloon wrapped with a nylon mesh. There are several sizes of the Inoue balloon, and because of its compliance, the balloon size can vary up to 4 mm in diameter. Balloon size selection is based on the patient's height. The catheter valve is elongated on insertion through the femoral vein.

After transseptal catheterization and dilation of the interatrial septum, the patient should receive therapeutic anticoagulation with intravenous heparin, and a wire is placed into the left atrium to facilitate placement of the balloon. After the balloon is advanced into the left atrium, it is steerable to enable crossing of the stenotic mitral valve. When inflated, the balloon has a sequential inflation of the distal part of the balloon followed by the entire balloon. The balloon has a characteristic hourglass or dumbbell

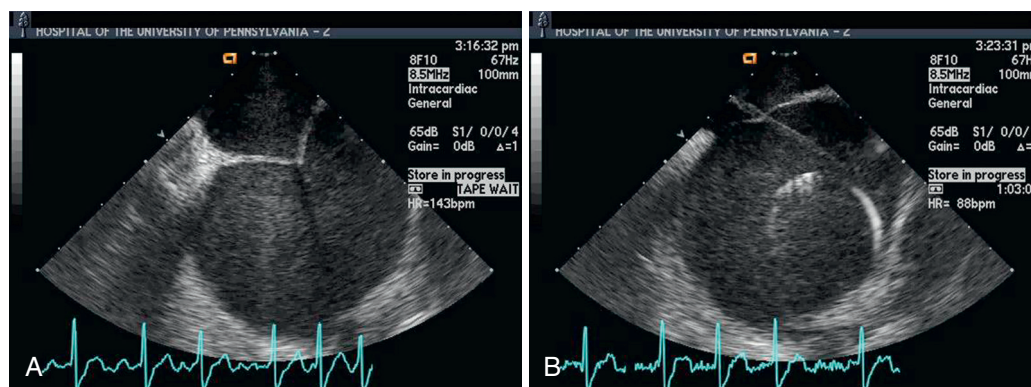


FIGURE 30.6 Intracardiac echocardiography (ICE) images of transseptal puncture. **A**, ICE image of the Brockenbrough needle tenting the interatrial septum. **B**, ICE image of the Mullins sheath and guidewire across the interatrial septum into the left atrium.

shape that allows for positioning and stabilization. The balloon is compliant, allowing for incremental increase in balloon dilation size without the need to exchange for a larger size.

After the Inoue balloon has crossed the interatrial septum, the guidewire can be exchanged for a torque-able stylet, which is inserted into the balloon catheter. With the image intensifier in the 20- to 30-degree RAO position, the stylet can be used to align the balloon with the mitral valve orifice, usually with a counterclocking (anterior deflection) motion. At this point, the balloon catheter can be advanced across the mitral valve orifice the distal portion of the balloon is inflated. With inflation of the distal portion of the balloon (across the mitral orifice), the balloon is gently withdrawn back until it straddles the mitral orifice (using fluoroscopic and TEE guidance). At this point, the balloon is fully inflated for 4 to 5 seconds and rapidly deflated. After deflation, the balloon is withdrawn to the left atrium (Figure 30.7).

After balloon inflation, the stylet can be removed and the balloon catheter can be attached to a pressure transducer (with care so as not to introduce air) to monitor LA pressure. TEE can be used to assess valve gradients, morphology, and degree of MR. Direct measurements of gradients with the catheters in both the LA and LV can provide information about residual gradients. A reduction in mean MV gradient by 50% or an increase in MVA greater than 1.5 cm² is considered a successful result. An increase in MR by more than 1 grade after balloon inflation should signal ending the procedure despite residual gradients. As such, it is important to carefully evaluate for severe commissural calcium preprocedurally. Calcium does not split with balloon inflation but increases the potential for tearing the leaflet, creating MR.

Double-Balloon Technique

The double-balloon technique is less widely used and has been mostly replaced by the Inoue technique, in part because of the lack of risk of LV perforation with the Inoue balloon. After transseptal catheterization and therapeutic

anticoagulation, a balloon-tipped end-hole catheter is used to traverse the mitral valve via the transseptal puncture site. This catheter is navigated to the apex of the left ventricle, and after it has been positioned, a 260-cm guidewire is placed in the LV apex. The wire can also be tracked and placed into the descending aorta, although is certainly more time consuming. A second guidewire is placed using a similar technique or by using a dual-lumen catheter. An 18- or 20-mm dilation balloon is tracked and positioned on each wire and then advanced across the mitral valve orifice and inflated simultaneously to dilate the valve.^{13,14}

Results

With PMBV, the initial success rate (MVA of >1.5 cm² and a decrease in LA pressure <18 mm Hg, without complications) in selected patients exceeds 80%. Over the long term, survival and event-free survival after PMBV are influenced by valve morphology reflected by a Wilkins echo score greater than 8. In 879 patients who underwent PMBV with a mean follow-up of 4.2 ± 3.7 years, in patients with Wilkins echo scores below 8, there was a greater immediate increase in MVA after PMBV ($P < .0001$) and improved long-term survival (82% vs 57%; $P < .0001$) in these patients. These patients with higher echo scores also have higher events in the long term, including need for repeat PMBV, need for mitral valve surgery, and death. In a multivariate analysis, age, after PMBV an MR grade of 3+ or more, prior surgical commissurotomy, New York Heart Association (NYHA) Class IV symptoms, and elevated post-PMBV PASPs were all independently associated with worse outcome at follow-up.¹⁵

Before PMBV, surgical commissurotomy was the surgical treatment for patients with symptomatic MS. With the advent of cardiopulmonary bypass, commissurotomy was performed as an open operation. Two studies examined a longer term comparison between open commissurotomy versus PMBV. Cotrufo et al.¹⁶ examined 193 patients (111 PMBV with Inoue technique) who underwent either PMBV or open commissurotomy with a mean follow-up period of 37 ± 22.9 months and a mean age of 46.5 ± 13.8 years.

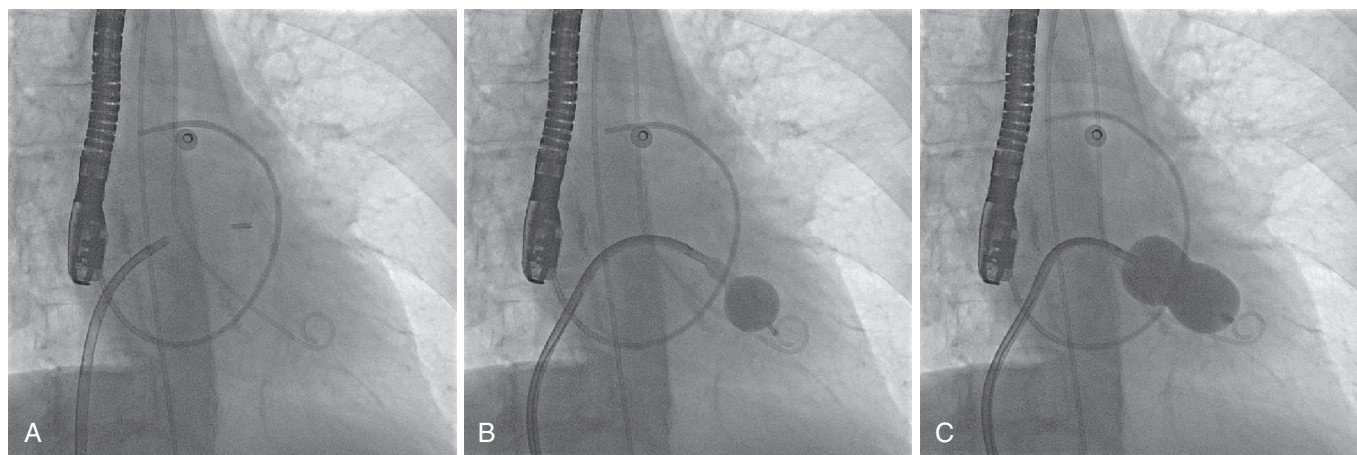


FIGURE 30.7 **A**, Fluoroscopic image demonstrating an Inoue balloon positioned across the atrial septum positioned in the left atrium. Also note a pigtail catheter in the left ventricle, a Swan-Ganz catheter in right pulmonary artery, and a transesophageal echocardiogram probe for procedural imaging. **B**, Fluoroscopic image of inflation of the distal end of the Inoue balloon, and the balloon straddling the mitral valve orifice before complete inflation. **C**, Fluoroscopic image of complete inflation of the Inoue balloon across a stenotic mitral valve during a balloon mitral valvuloplasty procedure.

The mean echo score in the PMBV group was 7.63 ± 1.9 and was 8.18 ± 1.93 in the surgical group. At follow-up, both groups had similar risk and incidence of complications; however, those undergoing surgery had larger MVAs and better functional recovery.¹⁶ A study by Ben Farhat et al.¹⁷ compared PMBV, open commissurotomy, and closed commissurotomy. In this analysis, the mean patient age was lower, and the mean echo score was lower than in the Cotrufo et al.¹⁶ study. At 7-year follow-up, open commissurotomy (30 patients) and PMBV (30 patients) had comparable results in a more favorable patient population for PMBV.

The most common complication from PMBV is severe MR, which can occur in 2% to 10% of procedures. The rates of severe MR after PMBV are not significantly different between the Inoue and double-balloon techniques.¹⁸ The overall procedural mortality rate is approximately 1%. Other less common procedural complications include pericardial tamponade, embolic events, vascular complications, arrhythmias, bleeding, stroke, myocardial infarction, residual atrial septal defect, and LA perforation. Because of the technically challenging nature of the procedure, operator experience should be taken into account when considering procedural success and complication rates.

Procedural Imaging

The use of procedural imaging beyond fluoroscopy can assist interventional operators to safely and effectively perform the PMBV procedure. Imaging is also helpful in the assessment of postprocedural results and complications such as acute severe MR. TEE is commonly used to guide the interventional procedure. Optimal TEE views can help facilitate balloon positioning during PMBV. Furthermore, TEE can be used to confirm residual gradients and assess postinflation MR. This information may be of value in deciding for or against additional balloon inflation. Three-dimensional (3D) TEE can provide a “surgeon’s view” of the mitral valve and the fused commissures. The use of 3D TEE has been shown to be superior to TTE in reducing fluoroscopy time and time from first transseptal puncture to first balloon inflation time.¹⁹ A scoring system has also been developed to assess the suitability of the mitral valve for PMBV as well.²⁰

An alternative to TEE is ICE. An ICE catheter can be placed in the contralateral femoral vein through a sheath and placed in the right atrium or right ventricle to help guide transseptal puncture and PMBV (Figure 30.8). Furthermore, ICE has been placed in the aorta via arterial access and has been shown to be safe and in most cases more helpful for the procedure than ICE positioned in the venous system.²¹ Ideally, the decision regarding which imaging modality should be used for the procedure should be based on operator experience and comfort and on patient-related factors. Optimal imaging guidance is of utmost importance for procedural success.

Special Consideration: Pregnancy

There are several potential patient-related issues that add complexity to the treatment of patients with severe rheumatic MS. Given the young age of onset of rheumatic heart disease in many populations, patients can present with

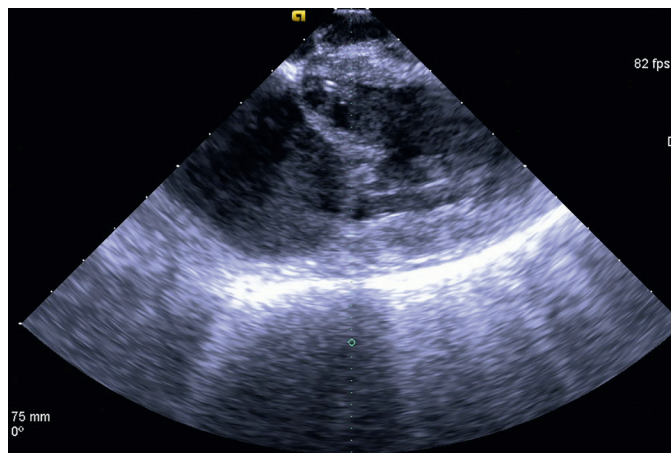


FIGURE 30.8 Intracardiac echocardiography (ICE) view of the left atrium, left ventricle, and a rheumatic mitral valve before percutaneous mitral balloon valvuloplasty for mitral stenosis. Note that the ICE catheter is positioned in the right ventricle to obtain this view.

symptoms during pregnancy. Pregnancy can exacerbate symptoms in patients with mild or moderate MS because of the increase in plasma volume and relative anemia. The resultant hemodynamic effects are decreased diastolic filling periods and increased mean transmitral pressure gradients. Mainstays of medical therapy for symptomatic patients include diuretic therapy and heart rate control. Caution must be used to select medications that are considered safe during pregnancy. Pregnant patients with severe MS should be referred to experienced centers for consideration of PMBV before delivery. The hemodynamic changes and fluid shifts that occur during delivery can lead to acute pulmonary edema, and appropriate careful monitoring of patients at the time of delivery is necessary.

MITRAL REGURGITATION

PATHOPHYSIOLOGY

Unlike MS, which is primarily caused by rheumatic fever, MR is a more diverse disease that results from dysfunction of any of the portions of the complex mitral valve apparatus, including the leaflets, chords, annulus, and left ventricle. It is often further classified as primary (organic or degenerative) disease, which primarily affects the leaflets (e.g., fibromuscular dysplasia, mitral valve prolapse, rheumatic disease), and secondary (ischemic or functional) diseases, which spare the leaflets (e.g., diseases of the atrium and ventricle, including ischemic dysfunction and dilated cardiomyopathy). Patients with severe MR have decreased survival times, whether symptomatic or not, and surgery is often recommended.²²⁻²⁴ In asymptomatic patients with preserved LV function, a “watchful waiting” approach until the development of symptoms, LV dysfunction, pulmonary hypertension, or atrial fibrillation can be considered.²⁵ Current guidelines recommend surgery for symptomatic patients and asymptomatic patients with abnormal LV function, and surgery may also be considered for asymptomatic patients with normal LV function when there is a high likelihood of successful repair.¹⁰

Rationale for Transcatheter Therapy

Surgery improves survival in observational studies,²⁶ but is associated with mortality rates of 1% to 5% and additional morbidity rates of 10% to 20%, including stroke, reoperation, renal failure, and prolonged ventilation.²⁷ The risks of surgery are particularly high older adults and patients who have LV dysfunction. In one study of more than 30,000 patients undergoing mitral valve replacement, the mortality increased from 4.1% in those younger than 50 years to 17.0% in octogenarians.²⁸ The risks of surgery, particularly in consideration of morbidity and patient preference, have stimulated attempts to develop less invasive solutions.²⁹

When considering percutaneous or transcatheter approaches for mitral repair, it is useful to classify them according to the major structural abnormality that they address.³⁰ Unlike the extensive toolbox available to mitral surgeons, transcatheter approaches are much more limited and often only able to address a single major element of the dysfunctional valve that contributes to MR.

Leaflet Repair with the MitraClip Device

MitraClip (Abbott Vascular) was the first transcatheter mitral valve repair technology to receive CE Mark approval and US Food and Drug Administration (FDA) approval for patients with primary (degenerative) MR and prohibitive surgical risk (Figure 30.9). This system replicates the Alfieri stitch operation, in which the middle scallops of the posterior and anterior leaflets (P2 and A2, respectively) are sutured together to create a double-orifice mitral valve (Videos 30.5 and 30.6). This operation, though usually performed with adjunctive ring annuloplasty, has proved effective and durable in a wide variety of pathologies as well as in selected patients without annuloplasty.^{31,32}

Trials with this device have confirmed its feasibility (EVEREST [Endovascular Valve Edge-to-Edge Repair Study] I), and its safety and efficacy were compared with those of surgical repair in a randomized trial (EVEREST II), providing a wealth of data on this technology.^{33,34} The procedure is performed with standard catheterization techniques using a transseptal approach from the right femoral vein.³⁵ The clip delivery system is introduced through a 24-Fr sheath into the left atrium, where it can be guided by TEE using a series of turning knobs under through the mitral valve into the left ventricle. A properly aligned and oriented clip can be placed on the P2 and A2 segments of leaflets, grasping them from the ventricular side to create leaflet opposition. After leaflet insertion is confirmed by echocardiography, the clip can be released. If a suboptimal grasp occurs, the leaflet can be released, allowing repositioning before a second grasp attempt. Additionally, a second or more clips can be placed as needed for optimal MR reduction.³⁵

In the 2:1 randomized EVEREST II trial, 184 patients were designated to receive MitraClip therapy and 95 to undergo surgical repair or replacement. These patients were almost a decade older (mean age, 67 years) than in usual surgical series and had more comorbidities. Major adverse events at 30 days were significantly less frequent with MitraClip therapy (9.6% vs 57% with surgery; $P < .0001$), although much of the difference could be attributed to the greater need for blood transfusions with surgery.³⁶ The freedom from the combined outcome of death, mitral valve surgery, and MR severity greater than 2+ at 12 months was higher with surgery (73%) than with MitraClip therapy (55%; $P = 0.0007$). Importantly, in patients with acute MitraClip therapy success, the result appears durable with a very low rate of later mitral valve surgery.

Subsequent analyses of this rich database have demonstrated persistent reductions in MR grade, improvement in

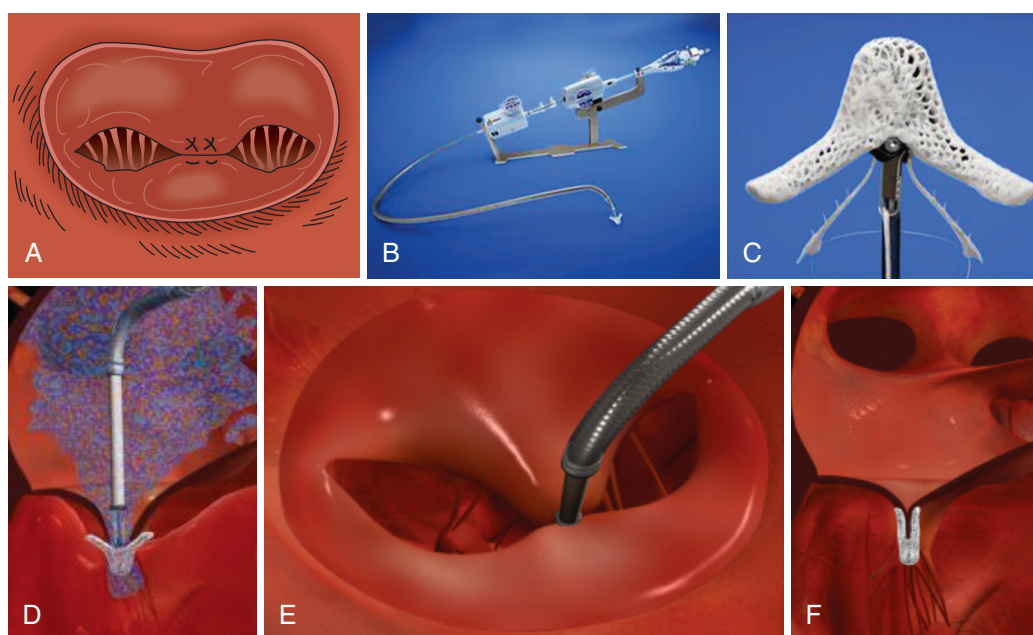


FIGURE 30.9 The MitraClip leaflet coaptation system. This device (Abbott Vascular, Inc.) creates a bridge between the P2 and A2 segments of the mitral valve similar to the Alfieri stitch operation (A) using a clip delivery system (B) and the MitraClip (C). D and E, Side view and left atrial view of the clip delivery system as it is advanced through the mitral valve in the open position before grasping of the leaflets. F, The final result after the clip has been released and the delivery system removed. (From Transcatheter mitral valve repair and replacement. In Otto CM, Bonow RO, eds. *Valvular Heart Disease*. 4th ed. Elsevier;2013:342.)

NYHA functional class, and reduction in LV dimensions with MitraClip therapy.³⁶ Other studies have demonstrated a lack of MS, no effect of initial rhythm on results, and benefit in higher risk patients.³⁷⁻³⁹

Most recently, Lim and colleagues⁴⁰ reported on 127 high-risk patients with degenerative MR with 1-year follow-up. The patients were older (mean age, 82 years) and at high surgical risk (STS score, 13.2). The 30-day mortality rate was lower than predicted (6.3%), and 83% of surviving patients had MR less than 2+ at 1 year with reduced LV volumes and improved quality of life. Importantly, there was a 73% reduction in hospitalization for heart failure in the year after MitraClip implantation compared with the year before MitraClip implantation.

As such, the ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease gives a Class 2a recommendation for transcatheter edge-to-edge repair (TEER) for degenerative MR in patients with favorable anatomy considered too high or prohibitive risk for surgery.⁴¹

Although the EVEREST II trial failed to demonstrate efficacy equivalent to that of surgery for a diverse group of patients with varied risk and cause, the EVEREST High-Risk Registry and Prohibitive-risk subset combined with the experience outside the United States pointed to a more appropriate role in high-risk patients with secondary functional and ischemic MR. Beyond primary MR, treatment of patients with secondary or functional MR poses an important challenge. In this setting, the disease process of ventricular dysfunction and enlargement results in papillary muscle displacement and annular dilatation with secondary effects on the mitral valve apparatus. Addressing the mitral valve itself as a strategy does not address the underlying cardiomyopathy. Surgery to repair the mitral valve is recommended at the time of coronary artery bypass grafting; however, there is little evidence to support isolated mitral valve surgery to improve survival in these patients, although symptomatic improvement is possible.⁴¹

The COAPT (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for High Surgical Risk Patients) trial was the first randomized clinical trial between TEER with the MitraClip system and guideline-directed medical therapy (GDMT) versus GDMT alone in 614 patients to show a meaningful benefit of TEER for functional MR. Patients treated TEER and GDMT demonstrated lower rates of heart failure hospitalizations and all-cause mortality at 2 years.⁴² In a previously published study, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR), TEER, 304 patients were randomized to TEER and medical therapy versus medical therapy alone; this study did not demonstrate a difference between treatment groups at 1 year.⁴³ The reason for differences between the two studies are thought to have led to differing outcomes, specifically the intensity of GDMT and differences in both valvular regurgitation severity and ventricular characteristics.⁴⁴ Despite these seemingly conflicting trial results, TEER with the MitraClip system received FDA approval and has a Class 2a recommendation in the ACC/AHA guidelines for the treatment of secondary MR in patients with suitable anatomy and severe MR despite being on optimal GDMT. The 3-year follow-up data from the COAPT study demonstrated a

sustained and durable reduction in MR with improved survival and quality of life.⁴⁵ Finally, there are several other devices designed to provide leaflet repair in either pre-clinical or phase 1 evaluation.

Indirect Annuloplasty

The venous anatomy of the heart is of particular interest for treating patients with MR because of the ease of access (from the right internal jugular vein) and the location of the great cardiac vein in proximity to the posterior mitral annulus. Some of the first attempts to treat patients with MR without surgery did so by mimicking surgical ring annuloplasty through placement of devices in the coronary sinus, so-called indirect or percutaneous coronary sinus annuloplasty. The goal of this approach is to remodel the posterior annulus, cinching the great cardiac vein or pushing in on the posterior annulus from the vein, to improve leaflet coaptation.

The CARILLON XE2 Mitral Contour System (Cardiac Dimensions, Inc.) has CE Mark and uses novel anchors placed permanently in the coronary sinus that are pulled toward each other with a cinching device to reduce the mitral annular dimension by traction (Figure 30.10). Early evaluation in the Amadeus study demonstrated feasibility, with implantation in 30 of 48 patients and modest improvement in quantitative measures of MR with a small risk of coronary compromise (15%) and death (1 patient).⁴⁶ More recently, a redesigned device was tested in the TITAN (Transcatheter Implantation of Carillon Mitral Annuloplasty Device) trial.⁴⁷ Among 65 enrolled participants with secondary MR (62% ischemic), the device was implanted successfully in 36 patients with a mean age of 62 years and a mean ejection fraction 29%, with predominantly NYHA functional Class III symptoms and with 2+ (30%), 3+ (55%), or 4+ (15%) grade MR. Quantitative measures of MR were better at 6 and 12 months than in 17 patients who were enrolled in the trial and did not receive implants.

In general, indirect annuloplasty devices may be able to provide modest MR reduction in selected patients but likely less than is achievable with surgery. Whether this level of efficacy will result in sufficient symptomatic improvement and LV remodeling to justify the procedure requires further study. The limited efficacy is related to the location of the coronary sinus relative to the annulus (≤ 10 mm more cranial), great individual anatomic variability, and the limited benefit of partial annular remodeling.^{2,48} Possibly, some “super-responders” may be able to be identified on the basis of anatomic considerations before the procedure.

The risks of this approach must also be considered. In addition to the risk for damage to the cardiac venous system, devices in this location can compress the left circumflex or diagonal coronary arteries that traverse between the coronary sinus and the mitral annulus in most patients.⁴⁹

In this regard, one novel indirect approach to reduce the septal-lateral dimension that deserves further consideration is the cerclage annuloplasty technique (see Figure 30.10). This approach attempts to create a more complete circumferential annuloplasty by placing a suture from the coronary sinus through a septal perforator vein into the right atrium or ventricle, where it is snared and

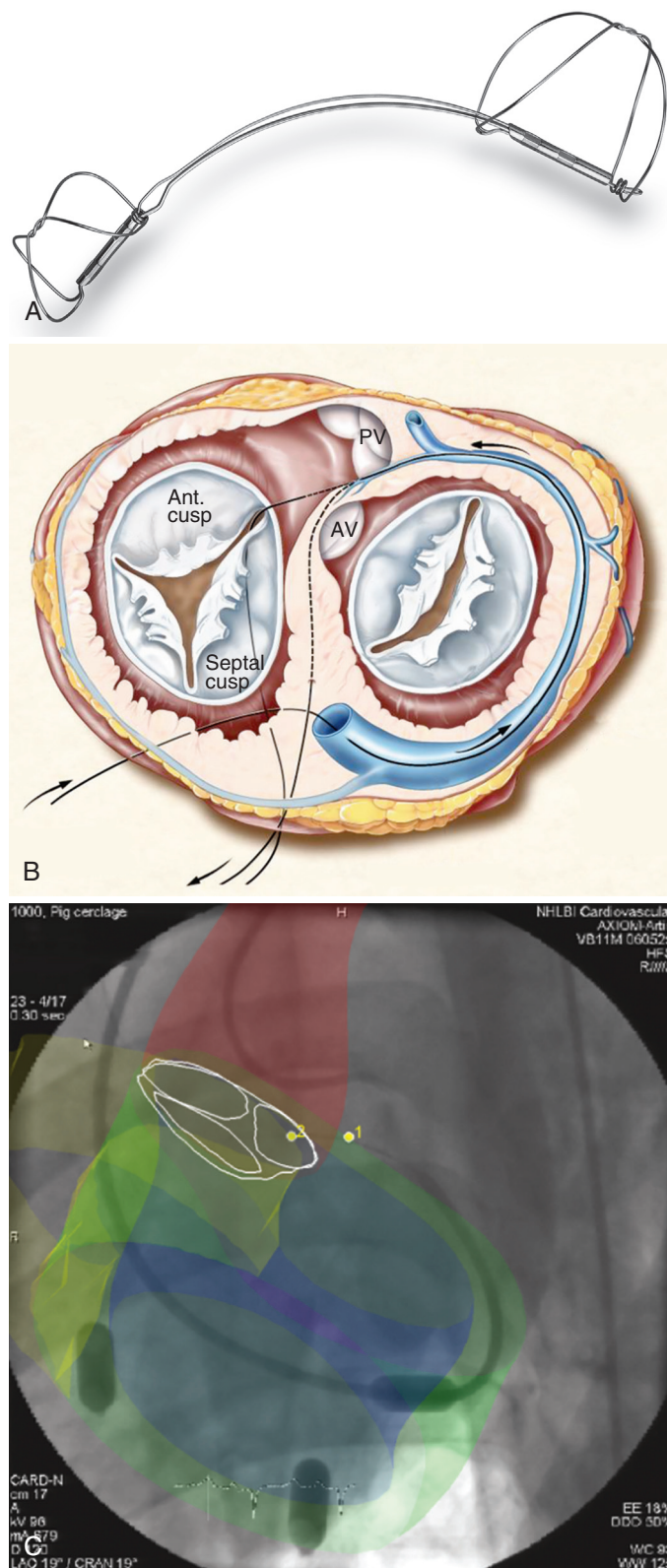


FIGURE 30.10 Several indirect annuloplasty devices. **A**, CARILLON XE2 Mitral Contour System (Cardiac Dimension, Inc.) coronary sinus cinching device. Cerclage technique, shown in a schematic (**B**), and an angiogram with superimposed magnetic resonance images (**C**). Ant, Anterior; AV, Aortic Valve; PV, Pulmonic valve. (**B** and **C**, from Kim JH, Kocaturk O, Ozturk C, et al. Mitral cerclage annuloplasty, a novel transcatheter treatment for secondary mitral valve regurgitation: initial results in swine. *J Am Coll Cardiol*. 54:638–651, 2009.) (From Transcatheter mitral valve repair and replacement. In Otto CM, Bonow RO, eds. *Valvular Heart Disease*. 4th ed. 346.)

tensioned with the proximal end from the right atrium to create a closed purse-string.⁵⁰ The procedure is guided by cardiac magnetic resonance imaging and uses a novel rigid protection device to avoid coronary compression.

Direct Annuloplasty and Left Ventricular Remodeling Techniques

Other devices have been developed to more directly remodel the mitral annulus, in part because of the limitations of indirect coronary sinus annuloplasty described earlier (Figure 30.11). The Mitralign Percutaneous Annuloplasty System (Mitralign, Inc.) was originally based on the surgical techniques of Paneth's posterior suture plication.⁵¹ In this procedure, a transaortic catheter is advanced to the left ventricle and is used to deliver pledgeted anchors through the posterior annulus that can be pulled together to shorten (plicate) the annulus up to 17 mm (with two implants). In 16 patients treated in a phase 1 trial, septal-lateral dimension could be reduced up to 8 mm.² A CE Mark trial is planned. The Accucinch (Guided Delivery Systems) device uses a similar catheter approach to place up to 12 anchors along the ventricular surface of the posterior mitral annulus. A cable running through the anchors is tensioned to create posterior placcation. In a later development, the anchors have been placed in the ventricular myocardium just below the valve plane (percutaneous ventriculoplasty). This device has been characterized as more of a ventricular remodeling approach than one that is truly annular (see Figure 30.11).

In addition to these devices that have entered clinical investigation, a preclinical device that deserves mention is the QuantumCor device (QuantumCor, Inc.). This technology uses low-radiofrequency energy delivered via a transseptal catheter (Boa RF Catheter) to shrink the collagen within the mitral annulus. In animals, a 20% to 25% reduction in anteroposterior dimension was achieved with a durability to 6 months. A first-in-human validation study during open-heart surgery is planned.

Finally, the Cardioband (Valtech Cardio) is an adjustable, catheter-delivered, sutureless device that is inserted transseptally or transatrially and anchored on the atrial side of the annulus with the potential for subsequent adjustment (see Figure 30.11). A successful first-in-human experience of 11 patients at three European centers with this device was recently reported.⁵² The Boston Scientific Millipede direct annuloplasty device is another catheter-delivered device delivered via transseptal access which is a semirigid complete ring and is being evaluated in the United States in an early feasibility study (NCT04147884).

The basis for devices to treat patients with MR by affecting the shape of the left ventricle arises from the pathophysiology of secondary ischemic or functional MR. Changes in the inferior and lateral left ventricle caused by infarction can lead to tethering or tenting of the posterior leaflet, allowing anterior leaflet override as the mechanism of MR.^{53,54} Similarly, failure of leaflet coaptation because of global LV enlargement causing annular distension is the major mechanism for MR in dilated cardiomyopathy.⁵⁵ Although ring annuloplasty can often ameliorate MR caused by LV distortion, procedures that specifically address the underlying LV

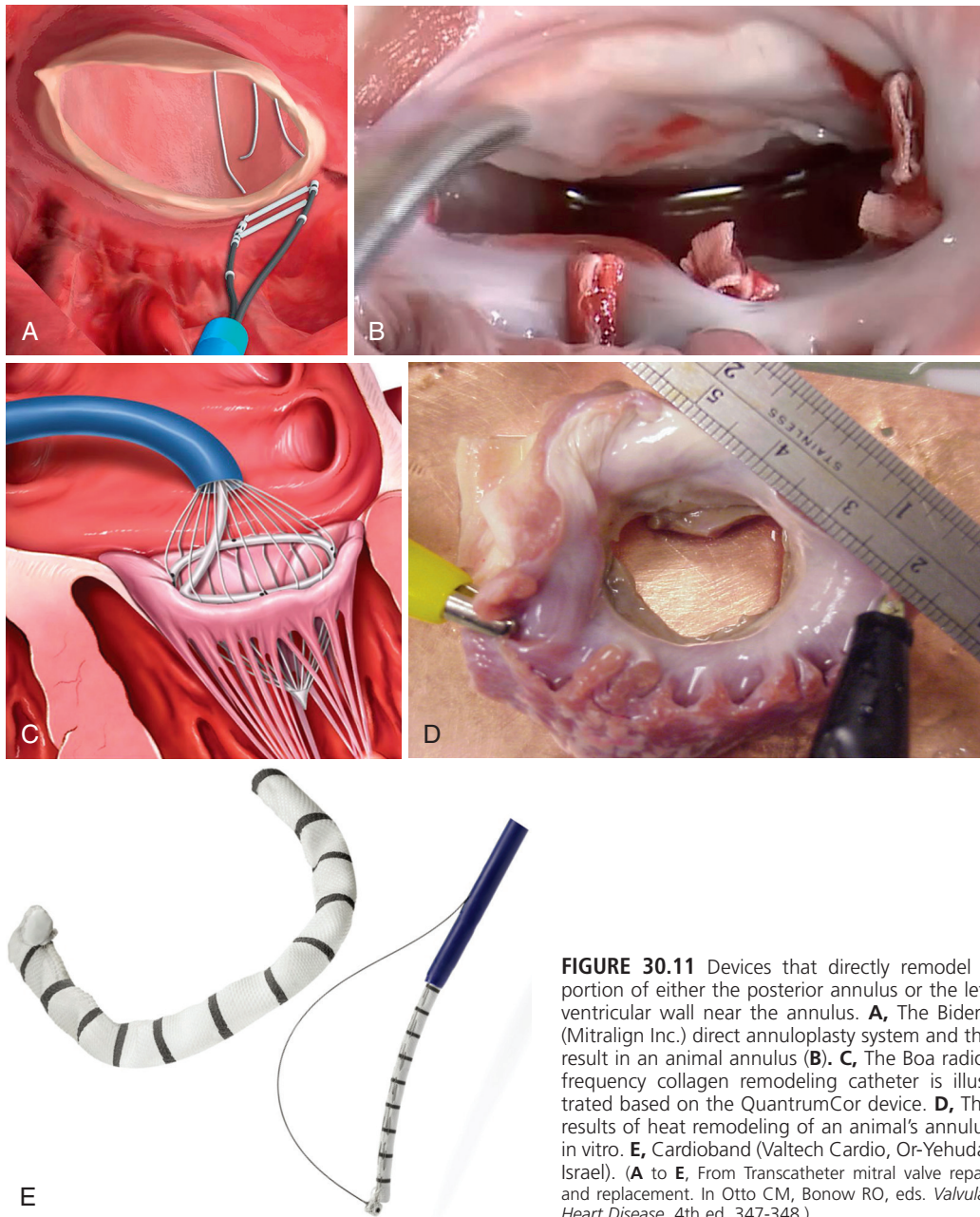


FIGURE 30.11 Devices that directly remodel a portion of either the posterior annulus or the left ventricular wall near the annulus. **A**, The Bident (Mitralign Inc.) direct annuloplasty system and the result in an animal annulus (**B**). **C**, The Boa radio-frequency collagen remodeling catheter is illustrated based on the QuantumCor device. **D**, The results of heat remodeling of an animal's annulus in vitro. **E**, Cardioband (Valtech Cardio, Or-Yehuda, Israel). (**A** to **E**, From Transcatheter mitral valve repair and replacement. In Otto CM, Bonow RO, eds. *Valvular Heart Disease*. 4th ed. 347-348.)

pathology may also be beneficial. The Basal Annuloplasty of the Cardia Externally (BACE) device (Mardil, Inc.) is a surgically implanted external tension band placed around the heart externally at the time of coronary artery bypass grafting revascularization to treat patients with ischemic MR. In a preliminary report of 11 patients treated in India, MR grade was reduced acutely from grade 3.3 to 0.6.

Transcatheter Mitral Valve Replacement

The rationale for transcatheter mitral valve replacement (TMVR) has as its basis several lessons learned from surgical valve replacement.⁵⁶ Surgical valve replacement is the most effective method to reliably reduce MR. This is particularly apparent in comparison with transcatheter repair, which does not appear to reduce MR to the same extent. Despite its proven efficacy, the risks of

surgery may include significant morbidity and mortality rates related to the incision and the need for cardiopulmonary bypass.^{27,28}

One of the touted advantages of surgical repair over replacement is the improved survival related to better LV remodeling.²⁶ However, this and other observational comparisons may be confounded by differences in patient baseline characteristics and comorbid conditions. In a recent randomized trial, 251 patients with severe ischemic MR underwent either surgical repair or chordal-sparing replacement.⁵⁷ At 12 months, there was no difference in the primary endpoint of LA end-systolic volume index, and there was more frequent recurrent MR in the repair group (32.6% with moderate or severe MR vs 2.3% with replacement). This finding provides further rationale to consider TMVR in this patient population as an alternative to open surgical repair.

Transcatheter mitral valve prostheses will first be used in older adults and other patients at high surgical risk for whom the benefits of repair are unproven or the anatomy is unfavorable and the risks of surgery are high. In this regard, early experience using transcatheter aortic valve

implantation devices in previously implanted and now degenerating surgical bioprostheses and rings has confirmed the feasibility of this approach (Table 30.1). Balloon-expandable prostheses have been implanted in degenerating bioprostheses⁵⁸⁻⁶³ and previous surgical annuloplasty

TABLE 30.1 Transcatheter Mitral Valve-in-Valve Implantation: Patient Characteristics and Outcomes of Trials of Transcatheter Mitral Valve Replacement in Patients with Valve-in-Valve, Valve-in-Ring, and Valve-in-Mitral Annular Calcification Using Commercially Available Transcatheter Heart Valves

	TARGET PATIENTS (N)	MEAN STS (%)	ACCESS	DEVICE	TECHNICAL SUCCESS RATE (%) ^a	SECOND VALVE (%)	LVOTO (%)	POSTPROCEDURAL MODERATE MR	OUTCOMES
Ye et al. ⁶⁷	73	9.6	—	100% Edwards Sapien	98.6	1.4	—	—	Overall 30-d mortality rate, 1.4%
	31 ViV mitral	9.7	—	—	—	3.2	—	—	Estimated overall survival rate at 1 y, 88.9%
	(42 ViV aortic)	(9.6)	—	—	—	—	—	—	—
Yoon et al. ⁶⁸	—	—	—	—	—	—	—	>Moderate	All-cause mortality at 30 d and 1 y
	248	8.9 ± 6.8	TS, 33.1 TA, 66.5 DA, 0.4	Balloon-expandable valves, 89.9	92.3	5.1	3.2	10.3%	All-cause mortality at 30 d and 1 y: 6.5%, 16.9%, respectively
	176 ViV	9.3 ± 7.0	TS, 35.2 TA, 64.2 DA, 0.6	—	96.0	2.8	2.3	6.8%	5.7%, 12.6%
	72 ViR	8.2 ± 6.3	TS, 27.8 TA, 72.2 DA, 0	—	83.3	11.1	5.6	19.4%	8.3%, 28.7%
Eield et al. ⁶⁹	87	—	TS, 100	Edwards, 100	90	6	9	—	All-cause mortality at 30 d and 1 y
	60 ViV	12.5 ± 7.2	—	—	97	2	5	—	95%, 86%
	15 ViR	11.4 ± 7.3	—	—	73	13	20	—	100%, 82%
	12 ViMAC	16.5 ± 12.0	—	—	75	17	17	—	83%, 57%
Guerrero et al. ⁷⁰	116 ViMAC	15.3 ± 11.6	TS, 40.5 TA, 39.7 DA, 19.8	98.2% Edwards Sapien	76.7	14.7	11.2	—	All-cause mortality at 30 d and 1 y, 25.0% and 53.7%
	—	—	—	Edwards Sapien	—	—	—	4.9%	25%, 53.7%
Yoon et al. ⁷¹	521	9.0 ± 7.0	TS, 39.5 TA, 59.5 DA, 1.0%	90.8% balloon expandable valves	87.1	5.4	7.1	—	All-cause mortality at 30 d and 1 y, 10.4%, 23.5%, respectively
	322 ViV	9.2 ± 7.2	TS, 38.8 TA, 59.9 DA, 1.2	—	94.4	2.5	2.2	5.6%	6.2%, 14.0%
	141 ViR	8.1 ± 6.4	TS, 35.5 TA, 64.5 DA, 0	—	80.9	12.1	5.0	18.4%	9.9%, 30.6%
	58 ViMAC	10.1 ± 6.9	TS, 53.4 TA, 44.8 DA, 1.7	—	62.1	5.2	39.7	13.8%	34.5%, 62.8%
	—	—	—	Edwards Sapien	—	—	—	13.8%	34.5%, 62.8%

TABLE 30.1 Transcatheter Mitral Valve-in-Valve Implantation: Patient Characteristics and Outcomes of Trials of Transcatheter Mitral Valve Replacement in Patients with Valve-in-Valve, Valve-in-Ring, and Valve-in-Mitral Annular Calcification Using Commercially Available Transcatheter Heart Valves—cont'd

	TARGET PATIENTS (N)	MEAN STS (%)	ACCESS	DEVICE	TECHNICAL SUCCESS RATE (%) ^a	SECOND VALVE (%)	LVOTO (%)	POSTPROCEDURAL MODERATE MR	OUTCOMES
Yoon et al. ⁷²	194	7.4	TS, 47.9 TA, 51.5 DA, 0.5	89.7	Balloon-expandable valves, 81.4	—	13.4	—	Procedural mortality rate, 6.7%
	107 ViV	7.3	TS, 43.9 TA, 55.1 DA, 0.9	—	94.4	—	1.9	—	1.9%
	50ViR	6.2	TS, 46.0 TA, 54.0 DA, 0	—	74.0	—	8.0	—	2.0%
	37 ViMAC	8.8	TS, 62.2 TA, 37.8 DA, 0	—	54.1	—	54.1	—	27.0%
Guerrero et al. ⁷³	903	10.0	TS, 43.1 TA, 44.8 DA, 0.3	Edwards Sapien, 96.1	87.9	3.7	2.3	1.4%	All-cause mortality at 30 d, 10.1%
	680 ViV	10.0	TS, 41.8 TA, 46.8 DA, 0.1	Edwards	90.9	1.5	0.7	1.1%	8.1%
	123 ViR	9.3	TS, 50.4 TA, 35.8	Sapien	82.9	7.3	4.9	2.4%	11.5%
	100 ViMAC	10.3%	TS, 43.0 TA, 42.0 DA, 2.0%	—	74	14	10	—	21.8%
Brian et al. ⁷⁴	1529 ViV	11.0	TS, 87TA, 13	Edwards Sapien3, 100	96.8	0	0.9	—	All-cause mortality at 30 d and 1 y; 5.4%, 16.7%, respectively
			TA, 13	100% Edwards Sapien 3	—	—	—	—	5.4%, 16.7%

DA, direct open transatrial approach; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; NYHA, New York Heart Association classification; STS, Society of Thoracic Surgeons; TA, transapical approach; THV, transcatheter heart valve; TS, transseptal approach; ViMAC, valve-in-mitral annular calcification; ViR, valve-in-ring; ViV, valve-in-valve.

^aTechnical success is defined using the Mitral Valve Academic Research Consortium criteria.²⁸

From Enta Y, Nakamura M. Transcatheter mitral valve replacement. *J Cardiol*. 2021;77(6):555-564.

rings⁶⁴⁻⁶⁶ predominantly via a transapical approach. However, the feasibility of transseptal delivery^{59,65,66} and transatrial^{59,61} delivery has also been demonstrated. Complications, including valve embolization, bleeding, and death, have been reported, but the early results have been generally favorable with excellent reduction in MR grade and low residual transmitral gradients.

There are several such TMVR platforms in various stages of development from early concept to pivotal clinical studies. The important design and patient selection challenges will have an impact on the success of the procedure. The access site for valve delivery is currently varied with devices using transapical, transfemoral transseptal, or transatrial access. Ultimately, transfemoral transseptal access will likely be the favored approach. Although transapical access has been used for transcatheter aortic valve replacement (TAVR), patients did not derive a similar benefit to those undergoing transfemoral procedures. It is likely that patients with functional or ischemic MR with depressed LV function may not derive similar

benefit over the long term with transapical access. Although transseptal access appears to be the ideal approach, there are important technical challenges in being able to design a delivery catheter and valve system to properly overcome the angulation and alignment issues necessary for valve delivery and deployment. Furthermore, unlike in TAVR in which the stented prosthesis can anchor to calcium for valve delivery, the absence of calcium in most of these cases requires unique designs to allow for proper anchoring of the valve. Additional challenges in the mitral valve include the noncircular shape and designing the proper prosthesis to properly fit and avoid paravalvular regurgitation. After positioning and anchoring are addressed, the issue of left ventricular outflow tract (LVOT) obstruction by the prosthesis and the anterior mitral valve leaflet will need to be considered.⁷⁵ Although techniques such as catheter-based laceration of the anterior mitral leaflet have been devised to help address this issue, it remains unclear whether there is a role for this with newer TMVR devices and how much

complexity it adds to the procedure.⁷⁶ Finally, given that these devices sit in the left atrium and have a large profile, the requirement and duration of anticoagulation for these patients will need to be considered.

The first transseptal device TMVR device in development is the Edwards Evoque platform, a transseptally inserted stent device with a foreshortening frame and LV anchors that grasp the mitral leaflets. An initial human study demonstrated feasibility in 14 patients with symptomatic moderate to severe MR of varied cause were treated with the Evoque system with a median age of 84 years and a median Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) of 4.6%.⁷⁷ There was a 93% procedural success rate and a 30-day 7.1% all-cause mortality rate. The MISCEND Study (Edwards EVOQUE Eos Mitral Valve Replacement: Investigation of Safety and Performance After Mitral Valve Replacement With Transcatheter Device) (NCT02718001) is a multicenter single-arm study underway evaluating the safety and performance of the Evoque Eos, the latest iteration of this TMVR system that is both repositionable and removable after it is deployed.

The Abbott Tendyne TMVR system is delivered via transapical access with the valve frame implanted into the mitral annulus and tethered to the apex of the left ventricle using an anchoring system. The Tendyne Global Feasibility Trial, a single-arm prospective registry, examined the device for safety and effectiveness in 30 patients with varying types of MR with a mean age of 75.6 ± 9.2 years and STS PROM of $7.3\% \pm 5.7\%$.⁷⁸ Successful device implantation occurred in 93.3% of patients, and at 30 days, 86.6% of patients had successful device implantation without cardiovascular mortality, stroke, or device malfunction. In looking at the first 100 patients treated in this study, technical success was achieved in 96% of the patients, and the 1-year survival rate free of all-cause mortality was 72.4% with important improvements in quality of life at 1 year.⁷⁹ The device has achieved CE Mark approval in Europe. The SUMMIT trial (Clinical Trial to Evaluate the Safety and Effectiveness of Using the Tendyne Transcatheter Mitral Valve System for the Treatment of Symptomatic Mitral Regurgitation) (NCT03433274) is currently enrolling patients in a three-arm study, a randomized (1:1 with MitraClip), nonrandomized (Tendyne TMVR only), and a nonrandomized cohort with mitral annular calcification (Tendyne TMVR only).

The Intrepid TMVR system (Medtronic) was initially designed via transapical access but has been modified into a transseptal delivery design. The valve is designed with a nitinol stent frame with a trileaflet valve mounted within. The initial 50-patient experience in patients with severe symptomatic MR deemed high or extreme risk for surgery (mean STS PROM $6.4\% \pm 5.5\%$) revealed successful implant in 96% of cases with 14% 30-day mortality rate and significant improvement in symptoms at follow-up.⁸⁰ The APOLLO trial (Transcatheter Mitral Valve Replacement With the Medtronic Intrepid™ TMVR System in Patients With Severe Symptomatic Mitral Regurgitation) (NCT 03242642) will enroll 1150 patients with moderate to severe symptomatic MR who are not suitable for surgery or TEER into one of two nonrandomized prospective cohorts. The primary cohort will be patients with primary or secondary MR treated with the Intrepid valve, and the mitral

annular calcification (MAC) cohort will treat patients with MAC with TMVR.

Several other TMVR systems are in various stages of development. The Tiara TMVR System (Neovasc Inc.) is a transapical TMVR system with a nitinol stent frame and a trileaflet bovine pericardial valve mounted on the frame. Currently, the program to develop this system is on hold. The Edwards Sapien M3 system uses a modified Sapien 3 TAVR valve delivery via transseptal access into a nitinol coiling docking system that wraps outside the mitral valve apparatus. This design may potentially help reduce the risk of LVOT obstruction. The 30-day outcomes of the first 35 patients treated revealed technical success in 88.6% of patients with a 30-day all-cause mortality rate of 2.9% and more than 87% of patients with 1+ or less MR.⁸¹ Several other TMVR systems are currently in various stages of development and investigation, including the transfemoral transseptal HighLife TMVR system currently undergoing feasibility study (NCT04029337) and the transfemoral transseptal AltaValve TMVR system also in an early feasibility study (NCT03997305).

Both transseptal and transapical insertion of mitral valve replacement prostheses may be an attractive future option for patients for whom surgery poses a high risk. The potential advantages of this approach include the avoidance of both the surgical incision and the effects of cardiopulmonary bypass. Such devices could be fully sparing of the subvalvular apparatus and provide MR reduction that is equivalent to that achieved with surgical valve replacement.

CONCLUSIONS

The complexity of the mitral valve apparatus and the myriad causes of MR have led the field of transcatheter mitral valve repair and replacement to develop more slowly than anticipated. Fueled by the ever-growing prevalence of heart failure in the aging US population⁸²—most of these older patients with heart failure have significant MR—and aided by clinical evidence from studies such as the COAPT trial and the ingenuity of physicians and engineers, transcatheter mitral valve therapies will probably also become an available option for such patients.

REFERENCES

1. Gorman JH III, Jackson BM, Enomoto Y, et al. The effect of regional ischemia on mitral valve annular saddle shape. *Ann Thorac Surg*. 2004;77(2):544-548.
2. Choure AJ, Garcia MJ, Hesse B, et al. In vivo analysis of the anatomical relationship of coronary sinus to mitral annulus and left circumflex coronary artery using cardiac multidetector computed tomography: implications for percutaneous coronary sinus mitral annuloplasty. *J Am Coll Cardiol*. 2006;48(10):1938-1945.
3. Chandrashekar Y, Westaby S, Narula J. Mitral stenosis. *Lancet*. 2009;374:1271-1283.
4. Guilherme L, Fae KC, Oshiro SE, et al. Rheumatic fever: how S. pyogenes-primed peripheral T cells trigger heart valve lesions. *Ann NY Acad Sci*. 2005;1051:132-140.
5. World Health Organization. *Rheumatic Fever and Rheumatic Heart Disease*. WHO Technical Report Series No 923. 2001. Available at: http://www.who.int/cardiovascular_diseases/resources/en/cvd_trs923.pdf.
6. Gordon SP, Douglas PS, Come PC, et al. Two-dimensional and Doppler echocardiographic determinants of the natural history of mitral valve narrowing in patients with rheumatic mitral stenosis: implications for follow-up. *J Am Coll Cardiol*. 1992;19:968-973.

7. Zipes DP, Libby P, Bonow RO, et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia: Elsevier Saunders; 2005: 1553-1564. 7th ed.
8. Wilkins GT, Weyman AE, Abascal VM, et al. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J*. 1988;60:299-308.
9. Aviles RJ, Nishimura RA, Pellikka PA, et al. Utility of stress Doppler echocardiography in patients undergoing percutaneous mitral balloon valvotomy. *J Am Soc Echocardiogr*. 2001;14:676-681.
10. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143:e72-e227.
11. Palacios IF, Block PC, Wilkins GT, et al. Follow-up of patients undergoing percutaneous mitral balloon valvotomy. Analysis of factors determining restenosis. *Circulation*. 1989;79:573-579.
12. Inoue K, Owaki T, Nakamura T, et al. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg*. 1984;87:394-402.
13. Al Zaibag M, Al Kasab S, Ribeiro PA, et al. Percutaneous double-balloon mitral valvotomy for rheumatic mitral valve stenosis. *Lancet*. 1986;1:757-761.
14. Palacios IF, Block PC, Brandt S, et al. Percutaneous balloon valvotomy for patients with severe mitral stenosis. *Circulation*. 1987;75:778-784.
15. Palacios IF, Sanchez PL, Harrell LC, et al. Which patients benefit from percutaneous mitral valvuloplasty? Prevalvuloplasty and postvalvuloplasty variables that predict long-term outcome. *Circulation*. 2002;105:1465-1471.
16. Cotrufo M, Renzulli A, Ismeno G, et al. Percutaneous mitral commissurotomy versus open mitral commissurotomy: a comparative study. *Eur J Cardiothorac Surg*. 1999;15:646-651.
17. Farhat MB, Ayari M, Maatouk F, et al. Percutaneous balloon versus surgical closed and open mitral commissurotomy: seven-year follow-up results of a randomized trial. *Circulation*. 1998;97:245-250.
18. Ruiz CE, Zhang HP, Macaya C, et al. Comparison of Inoue single-balloon versus double-balloon technique for percutaneous mitral valvotomy. *Am Heart J*. 1992;123:942-947.
19. Eng MH, Salcedo EE, Kim M, et al. Implementation of real-time three-dimensional transesophageal echocardiography for mitral balloon valvuloplasty. *Catheter Cardiovasc Interv*. 2013;82:994-998.
20. Anwar AM, Attia WM, Nosir YF, et al. Validation of a new score for the assessment of mitral stenosis using real-time three-dimensional echocardiography. *J Am Soc Echocardiogr*. 2010;23:13-22.
21. Akkaya E, Vuruskan E, Zorlu A, et al. Aortic intracardiac echocardiography-guided septal puncture during mitral valvuloplasty. *Eur J Cardiovasc Imaging*. 2014;15:70-76.
22. Bursi F, Enriquez-Sarano M, Nkomo VT, et al. Heart failure and death after myocardial infarction in the community: the emerging role of mitral regurgitation. *Circulation*. 2005;111:295-301.
23. Trichon BH, Felker GM, Shaw LK, et al. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Cardiol*. 2003;91:538-543.
24. Enriquez-Sarano M, Avierinos J-F, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med*. 2005;352:875-883.
25. Rosenhek R, Rader F, Klaar U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation*. 2006;113:2238-2244.
26. Enriquez-Sarano M, Schaff HV, Orszulak TA, et al. Valve repair improves the outcome of surgery for mitral regurgitation: a multivariate analysis. *Circulation*. 1995;91:1022-1028.
27. Gammie JS, O'Brien SM, Griffith BP, et al. Influence of hospital procedural volume on care process and mortality for patients undergoing elective surgery for mitral regurgitation. *Circulation*. 2007;115:881-887.
28. Mehta RH, Eagle KA, Coombs LP, et al. Influence of age on outcomes in patients undergoing mitral valve replacement. *Ann Thorac Surg*. 2002;74:1459-1467.
29. Masson JB, Webb JG. Percutaneous treatment of mitral regurgitation. *Circ Cardiovasc Interv*. 2009;2:140-146.
30. Chaim PTL, Ruiz CE. Percutaneous mitral valve repair: a classification of the technology. *J Am Coll Cardiol Interv*. 2011;4:1-13.
31. Alfieri O, Maisano F, De Bonis M, et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg*. 2001;122:674-681.
32. Maisano F, Caldarola A, Blasio A, et al. Midterm results of edge-to-edge mitral valve repair without annuloplasty. *J Thorac Cardiovasc Surg*. 2003;126:1987-1997.
33. Feldman T, Wasserman HS, Herrmann HC, et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST phase 1 clinical trial. *J Am Coll Cardiol*. 2005;46:2134-2140.
34. Herrmann HC, Feldman T. Percutaneous mitral valve edge-to-edge repair with the Evalve MitraClip System: rationale and phase 1 results. *EuroIntervention*. 2006;1(suppl A):A36-A39.
35. Silvestry FE, Rodriguez LL, Herrmann HC, et al. Echocardiographic guidance and assessment of percutaneous repair for mitral regurgitation with the Evalve MitraClip: lessons learned from EVEREST 1. *J Am Soc Echocardiogr*. 2007;20:1131-1140.
36. Feldman T, Foster E, Glower D, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364:1395-1406.
37. Herrmann HC, Kar S, Siegel R, et al. Effect of percutaneous mitral repair with the MitraClip device on mitral valve area and gradient. *EuroIntervention*. 2009;4:437-442.
38. Herrmann HC, Gertz ZM, Silvestry FE, et al. Effects of atrial fibrillation on treatment of mitral regurgitation in the EVEREST II randomized trial. *J Am Coll Cardiol*. 2012;59:1312-1319.
39. Whitlow PL, Feldman T, Pedersen WR, et al. Acute and 12-month results with catheter-based mitral valve leaflet repair. *J Am Coll Cardiol*. 2012;59:130-139.
40. Lim DS, Reynolds MR, Feldman T, et al. Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation after transcatheter mitral valve repair. *J Am Coll Cardiol*. 2014;64:182-192.
41. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77(4):e25-e197.
42. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379(24):2307-2318.
43. Obadia J-F, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379(24):2297-2306.
44. Nishimura RA, Bonow RO. Percutaneous repair of secondary mitral regurgitation—a tale of two trials. *N Engl J Med*. 2018;379(24):2374-2376.
45. Mack MJ, Lindenfeld J, Abraham WT, et al. 3-year outcomes of transcatheter mitral valve repair in patients with heart failure. *J Am Coll Cardiol*. 2021;77(8):1029-1040.
46. Schofer J, Siminiak T, Haude M, et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. *Circulation*. 2009;120:326-333.
47. Lipiecki J, Siminiak T, Sievert H, et al. Coronary sinus based percutaneous annuloplasty as treatment for functional mitral regurgitation: The TITAN II trial. *Open Heart (BMJ)*. 2016;3:e000411.
48. Maselli D, Guarracino F, Chiamonti F, et al. Percutaneous mitral annuloplasty: an anatomic study of human coronary sinus and its relation with mitral valve annulus and coronary arteries. *Circulation*. 2006;114:377-380.
49. Sponga S, Bertrand OF, Philippon F, et al. Reversible circumflex coronary artery occlusion during percutaneous transvenous mitral annuloplasty with the Viacor system. *J Am Coll Cardiol*. 2012;59:288.
50. Kim J-H, Kocaturk O, Ozturk C, et al. Mitral cerclage annuloplasty, a novel transcatheter treatment for secondary mitral valve regurgitation: initial results in swine. *J Am Coll Cardiol*. 2009;54:638-651.
51. Tibayan FA, Rodriguez F, Liang D, et al. Paneth suture annuloplasty abolishes acute ischemic mitral regurgitation but preserves annular and leaflet dynamics. *Circulation*. 2003;108(suppl II):II-128-II-133.
52. Nombela-Franco L, Urena M, Ribeiro B, Rodes-Cabau J. Advances in percutaneous treatment of mitral regurgitation. *Rev Esp Cardiol*. 2013;66(7):566-582.
53. Chaput M, Handschumacher MD, Tournoux F, et al. Mitral leaflet adaptation to ventricular remodeling: occurrence and adequacy in patients with functional mitral regurgitation. *Circulation*. 2008;118:845-852.
54. Silbiger JJ. Mechanistic insights into ischemic mitral regurgitation: echocardiographic and surgical implications. *J Am Soc Echocardiogr*. 2011;24:707-719.
55. Komeda M, Glasson JR, Bolger AF, et al. Geometric determinants of ischemic mitral regurgitation. *Circulation*. 1997;96(suppl):II-128-II-133.
56. Herrmann HC. Transcatheter mitral valve implantation. *Cardiac Interv Today*. 2009;82-85.
57. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med*. 2014;370:23-32.
58. Seiffert M, Franzen O, Conradi L, et al. Series of transcatheter valve-in-valve implantations in high-risk patients with degenerated bioprostheses in aortic and mitral position. *Catheter Cardiovasc Interv*. 2010;76:608-615.
59. Webb JG, Wood DA, Ye J, et al. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. *Circulation*. 2010;121:1848-1857.
60. Cerillo AG, Chiamonti F, Murzi M, et al. Transcatheter valve in valve implantation for failed mitral and tricuspid bioprostheses. *Catheter Cardiovasc Interv*. 2011;78:987-995.
61. Cheung AW, Gurvitch R, Ye J, et al. Transcatheter transapical mitral valve-in-valve implantations for a failed bioprosthesis: a case series. *J Thorac Cardiovasc Surg*. 2011;141:711-715.
62. Van Garsse LAFM, Gelsomino S, Van Ommen V, et al. Emergency transthoracic transapical mitral valve-in-valve implantation. *J Interv Cardiol*. 2011;24:474-476.
63. Gaia DF, Palma JH, de Souza JAM, et al. Transapical mitral valve-in-valve implant: an alternative for high risk and multiple reoperative rheumatic patients. *Int J Cardiol*. 2012;154:e6-e7.
64. de Weger A, Ewe SH, Delgado V, et al. First-in-man implantation of a transcatheter aortic valve in a mitral annuloplasty ring: novel treatment modality for failed mitral valve repair. *Eur J Cardiothorac Surg*. 2011;39:1054-1056.
65. Himbert D, Brochet E, Radu C, et al. Transseptal implantation of a transcatheter heart valve in a mitral annuloplasty ring to treat mitral repair failure. *Circ Cardiovasc Interv*. 2011;4:396-398.
66. Himbert D, Descoutures F, Brochet E, et al. Transvenous mitral valve replacement after failure of surgical ring annuloplasty. *J Am Coll Cardiol*. 2012;60:1205-1206.
67. Guerrero M, Dvir D, Himbert D, et al. Transcatheter mitral valve replacement in native mitral valve disease with severe mitral annular calcification: results from the first multicenter global registry. *JACC Cardiovasc Interv*. 2016;9(13):1361-1371.
68. Khan JM, Babaliaros V, Greenbaum AB, et al. Anterior leaflet laceration to prevent ventricular outflow tract obstruction during transcatheter mitral valve replacement. *J Am Coll Cardiol*. 2019;73(20):2521-2534.
69. Webb J, Hensley M, Fam N, et al. Transcatheter mitral valve replacement with the transseptal EVOQUE system. *JACC Cardiovasc Interv*. 2020;13(20):2418-2426.

70. Muller DW, Farivar RS, Jansz P, et al. Transcatheter mitral valve replacement for patients with symptomatic mitral regurgitation: a global feasibility trial. *J Am Coll Cardiol*. 2017;69(4):381-391.
71. Sorraja P, Moat N, Badhwar V, et al. Initial feasibility study of a new transcatheter mitral prosthesis: the first 100 patients. *J Am Coll Cardiol*. 2019;73(11):1250-1260.
72. Bapat V, Rajagopal V, Meduri C, et al. Early experience with new transcatheter mitral valve replacement. *J Am Coll Cardiol*. 2018;71(1):12-21.
73. Makkar R, O'Neill W, Whisenant B, et al. TCT-8 updated 30-day outcomes for the US early feasibility study of the SAPIEN M3 transcatheter mitral valve replacement system. *J Am Coll Cardiol*. 2019;73:1239-1246.
74. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics—2021 update. A report from the American Heart Association. *Circulation*. 2021;143(8):e254-e743.
75. Ye J, Cheung A, Yamashita M, et al. Transcatheter Aortic and Mitral Valve-in-Valve Implantation for Failed Surgical Bioprosthetic Valves: An 8-Year Single-Center Experience. *JACC Cardiovasc Interv*. 2015;8(13):1735-1744. doi:10.1016/j.jcin.2015.08.012.
76. Yoon SH, Whisenant BK, Bleiziffer S, et al. Transcatheter Mitral Valve Replacement for Degenerated Bioprosthetic Valves and Failed Annuloplasty Rings. *J Am Coll Cardiol*. 2017;70(9):1121-1131.
77. Eleid MF, Whisenant BK, Cabalka AK, et al. Early outcomes of percutaneous transvenous transseptal transcatheter valve implantation in failed bioprosthetic mitral valves, ring annuloplasty, and severe mitral annular calcification. *JACC Cardiovasc Interv*. 2017;10:1932-1942.
78. Guerrero M, Urena M, Himbert D, et al. 1-Year Outcomes of Transcatheter Mitral Valve Replacement in Patients With Severe Mitral Annular Calcification. *J Am Coll Cardiol*. 2018;71(17):1841-1853. doi:10.1016/j.jacc.2018.02.054.
79. Yoon SH, Whisenant BK, Bleiziffer S, et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. *Eur Heart J*. 2019;40(5):441-451. doi:10.1093/eurheartj/ehy590.
80. Yoon SH, Bleiziffer S, Latib A, et al. Predictors of Left Ventricular Outflow Tract Obstruction After Transcatheter Mitral Valve Replacement. *JACC Cardiovasc Interv*. 2019;12(2):182-193. doi:10.1016/j.jcin.2018.12.001.
81. Guerrero M, Vemulapalli S, Xiang Q, et al. Thirty-Day Outcomes of Transcatheter Mitral Valve Replacement for Degenerated Mitral Bioprostheses (Valve-in-Valve), Failed Surgical Rings (Valve-in-Ring), and Native Valve With Severe Mitral Annular Calcification (Valve-in-Mitral Annular Calcification) in the United States: Data From the Society of Thoracic Surgeons/American College of Cardiology/Transcatheter Valve Therapy Registry. *Circ Cardiovasc Interv*. 2020;13(3):e008425. doi:10.1161/CIRCINTERVENTIONS.119.008425.
82. Whisenant B, Kapadia SR, Eleid MF, et al. One-Year Outcomes of Mitral Valve-in-Valve Using the SAPIEN 3 Transcatheter Heart Valve. *JAMA Cardiol*. 2020;5(11):1245-1252. doi:10.1001/jamacardio.2020.2974.



Transcatheter Tricuspid Valve Intervention

SAIF ANWARUDDIN AND HOWARD C. HERRMANN

TRICUSPID VALVE REGURGITATION, 573
PATHOPHYSIOLOGY, 573
RATIONALE FOR THERAPY, 573
TRANSCATHETER TRICUSPID VALVE
INTERVENTION DEVICES, 574

LEAFLET-BASED REPAIR
TECHNOLOGY, 574
ANNULOPLASTY DEVICES, 575
SPACER DEVICES, 575

TRICUSPID VALVE REPLACEMENT, 575
CONCLUSION, 576

TRICUSPID VALVE REGURGITATION

Tricuspid regurgitation (TR) is a highly prevalent form of valvular heart disease affecting millions of patients. It is estimated that close to 1.6 million patients have a diagnosis of TR in the United States, and this is expected to increase with an aging population.¹ The predominant form of TR at clinical presentation (>85%) is functional in nature. Isolated TR caused by valvular or congenital disease accounts for the remainder of patients. Finally, pacemaker or defibrillator leads and transvenous lead extraction are also associated with tricuspid valve (TV) damage and TR.^{2,3}

Previously believed to be a marker of more advanced cardiovascular disease, we now appreciate that TR is independently associated with higher mortality.^{4,5} Furthermore, Doppler-based echocardiographic analysis has suggested worse outcomes on the basis of less than severe degrees of TR arguing in favor of earlier intervention.⁶

Despite the burden of disease and poor outcomes in medically managed patients, many are not offered potentially curative TV surgery. Most series have suggested that about 5000 operations are performed in North America each year for TV disease, with the vast majority of these being performed in the context of other cardiac surgery.⁷ Isolated TV surgery is performed even less commonly despite an observed increase over the course of a decade with the highest number of isolated TV surgeries performed at 780 in 2013.⁸ This series reported an in-hospital mortality rate of 8.8% for isolated TV surgery. Other series have reported similar in-hospital and higher longer-term mortality rates after isolated TV surgery.^{7,9,10} Although more contemporary series have identified improved outcomes after TV surgery,¹¹ reluctance to refer for isolated TV surgery is likely influenced by outcomes with higher morbidity and mortality. Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines¹² for management of TV regurgitation are not supported by high-quality evidence, and randomized clinical trials to support interventions are needed.

The reluctance to refer patients for TV surgery earlier in their course results in late clinical referrals characterized by refractoriness to medical therapies and higher rates of related complications, including liver and renal failure, worsening right ventricular (RV) dysfunction, and worsening frailty. As such, these patients are often not offered TV surgery because of their clinical conditions and worse clinical outcomes given the advanced stage of disease and medical comorbidities. For these reasons, the role for less invasive catheter-based approaches to address TR has gained acceptance given the need to address the burden of disease.

PATHOPHYSIOLOGY

Because the vast majority of TR occurs as secondary to other causes, it is important to consider the pathophysiology. Left-sided heart disease, pulmonary hypertension or atrial fibrillation, can lead to changes in RV function and, in certain cases, increases in RV afterload. Consequent RV remodeling occurs, which leads to tricuspid annular dilatation or leaflet tethering. Disruption of the TV anatomy results in functional or secondary TR.¹³ The presence of worsening long-standing severe TR leads to right-sided volume overload and effects on the liver and kidneys. This in turn leads to further volume overload and subsequent RV dilatation and dysfunction, leading to further tricuspid annular dilation and leaflet tethering, making the TR worse. Repair or replacement of the TV early on in this process is necessary to stop perpetuation of this cycle.

RATIONALE FOR THERAPY

The ACC/AHA Valvular Heart Disease Guidelines provide a Class I recommendation for surgical treatment of severe TR only in the setting of concomitant left-sided valve surgery.¹² Concomitant TR surgery, although demonstrated to be safe and effective, is also associated with improved right-sided remodeling over time.¹⁴ For patients with right

heart failure and isolated TR or secondary TR refractory to medical therapy and in the absence of pulmonary hypertension or left-sided disease, the guidelines provide a level 2a recommendation for TV surgery. In cases of prior left-sided valve surgery, TV surgery for severe TR and right heart failure is given a level 2b recommendation. This creates a conundrum because there is evidence to support the fact that even moderate TR is independently associated with increased mortality rates.¹⁵

The advantage of transcatheter-based tricuspid valve intervention (TTVI) over surgery as a less invasive but effective therapeutic strategy has led to an increased interest in novel devices for this unmet need. The goals of TTVI are effective TR reduction with a safer and less invasive approach and hopefully improved in-hospital and longer term outcomes than those offered by TV surgery. In addition, TTVI allows the TV to be addressed after left-sided surgery or in cases of isolated TR without concomitant left-sided disease with the hopes of preserving end-organ function and easing the burden of disease in patients. The other potential advantage of TTVI is the ability to offer the treatment to patients earlier in their disease process to avoid progression of disease and heart failure. Both novel repair and replacement devices are being actively examined in early feasibility and pivotal clinical studies. However, the data available thus far are from smaller single-arm series.

Because the clinical presentation of TR is most commonly functional TR, it is important to understand the effects of the disease process on the surrounding structures, including the TV annulus and the right ventricle. This may have potential important implications for not only device design but also the proper device selection for the patient. As an example, the structural changes to the right side of the heart in pulmonary hypertension-related functional TR are characterized by RV elongation and eccentricity, resulting in tethering of the TV leaflets, leading to malcoaptation. In contrast, in functional TR in the absence of

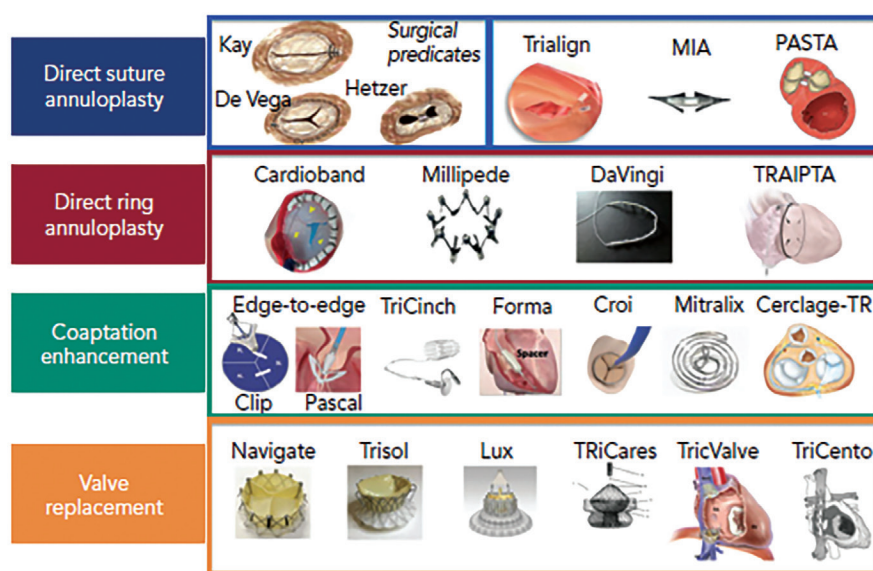
pulmonary hypertension, the right heart structural changes result in widening of the base of the RV and annular dilatation.¹⁶ Although TTVI spans both valve repair techniques and valve replacement options, part of the challenge moving forward in this area will be to understand which patients and which anatomic subsets are better suited for each. On the surgical side, both repair and replacement are potential options; however, surgical repair has been associated with lower mortality rates.^{17,18} In the TTVI space, understanding the advantages of repair versus replacement will be important as will identifying whether mortality rates differ among strategies. Figure 31.1 provides an illustration of several repair and replacement devices at various stages of development and investigation for the treatment of patients with TR.

TRANSCATHETER TRICUSPID VALVE INTERVENTION DEVICES

Repair strategies encompass annuloplasty, leaflet repair, and caval and spacer devices. Most of the experience thus far is early and limited to single-arm series with small numbers of patients, so the effectiveness and durability of these devices need further evaluation.

LEAFLET-BASED REPAIR TECHNOLOGY

Leaflet edge-to-edge repair approaches have been successful in the mitral valve space and are being evaluated for use for TV disease. The pivotal TRILUMINATE trial (Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System) (NCT03227757) is currently enrolling patients in a randomized, multicenter prospective study across the United



MIA = minimally invasive annuloplasty; PASTA = pledget-assisted suture tricuspid annuloplasty; TRAIPTA = transatrial intrapericardial tricuspid annuloplasty.

FIGURE 31.1 Transcatheter repair and replacement devices for tricuspid regurgitation. MIA, Minimally invasive annuloplasty; PASTA, pledget-assisted suture tricuspid annuloplasty; TRAIPTA, transatrial intrapericardial tricuspid annuloplasty. (From Curio J, Demir OM, Pagnesi M, et al. Update on the current landscape of transcatheter options for tricuspid regurgitation treatment. *Interv Cardiol.* 2019;14(2):54-61.)

States and Europe to evaluate the role for TriClip versus guideline-directed medical therapy in severe TR (Videos 31.1 and 31.2). The CLASP II TR trial (Edwards Pascal Transcatheter Valve Repair System in Tricuspid Regurgitation Pivotal Trial) (NCT04097145) is also enrolling patients with severe TR to either transcatheter repair with the Pascal Valve Repair System and optimal medical therapy versus optimal medical therapy only. One-year data from the single-arm initial registry of TriClip in 85 patients demonstrated that 71% of the patients experienced a reduction in TR to moderate or less and improvement in symptoms and quality of life with concomitant reverse remodeling of the right ventricle.¹⁹ In patients observed to have TR reduction after the procedure of moderate or less, survival was greater at 1 year ($P = .041$).

The TriValve registry examined the edge-to-edge repair in 249 patients in a multicenter, international single-arm registry for compassionate and off-label use.²⁰ Procedural success was achieved in 77% of patients, and more than half of the procedures were concomitant mitral and TV repair procedures. At 1 year, there was durable reduction in TR and an improvement in patient symptoms with an all-cause mortality rate of 20%.

ANNULOPLASTY DEVICES

Surgical annuloplasty with a rigid ring is an established method for surgical repair of the TV, and catheter-based methods have adopted this principle by using percutaneously delivered annuloplasty bands or other devices that serve to reduce the TV annulus size, specifically reduction of the septolateral annular diameter. The Edwards Cardioband Annular Reduction system is a catheter-based annuloplasty implant that is affixed on the annulus of the TV using a series of connected anchors. The TRI-REPAIR (Tricuspid Regurgitation Repair With Cardioband Transcatheter System) study examined the Cardioband system in a single-arm, multicenter prospective study enrolling 30 patients with moderate to severe functional TR.²¹ At 6 months, despite a 10% observed mortality rate, 76% of patients improved by at least one New York Heart Association (NYHA) functional class and overall 6-minute walk distance and quality of life metrics demonstrated significant improvement from baseline. This was accompanied by reductions in effective regurgitant orifice area (EROA) and mean vena contracta width in addition to reductions in septolateral diameters.

The MitraAlign TriAlign percutaneous system uses transjugular venous access to deploy an innovative suture-based annuloplasty system to plicate the posterior leaflet of the TV, thereby creating a two-leaflet valve (Kay procedure). The SCOUT trial (Percutaneous Tricuspid Valve Annuloplasty System for Symptomatic Chronic Functional Tricuspid Regurgitation) tested the safety and feasibility of the procedure in 15 patients in a single-arm, prospective, multicenter early feasibility study that demonstrated a technical success rate of 80%.²² In 12 patients who achieved technical success, there were significant reductions in annular diameter and EROA in addition to significant improvements in symptoms.

The 4TECH TriCinch device also attempts to replicate the Kay procedure using stent anchored into the inferior

vena cava and connected to an implant in the posterior leaflet, attempting to reduce the posterior leaflet. This study terminated before completing enrollment of patients in an early feasibility study (NCT03294200). Other annuloplasty devices being evaluated at various stages of development include the Millipede ring,²³ the transatrial intrapericardial tricuspid annuloplasty (TRAIPTA), and the Microinterventional Device minimally invasive annuloplasty (MIA) system (STTAR Study, NCT03692598).

SPACER DEVICES

The Edwards FORMA system is a unique device and the only one in this category. The device is positioned and anchored with the catheter tip in the RV apex and a spacer attached to the catheter, which allows the TV to coapt against it to reduce TR. Nineteen patients underwent the procedure in a multicenter single-arm experience.²⁴ At a median follow-up of 32 months, a 24% mortality rate was observed, but in survivors with successful implants, there was notable TR reduction and clinical symptomatic improvement; however, this device is no longer undergoing clinical evaluation at this time.

TRICUSPID VALVE REPLACEMENT

Tricuspid valve replacement (TTVR) for TR is in early stages of development and may hold several advantages over percutaneous repair strategies, particularly in patients with more advanced stages of disease. Because limited TR reduction leads to clinical benefit, it is important to consider that symptomatic clinical benefit is different than survival free of heart failure or overall survival. In the TriValve Registry, residual severe TR or greater was associated with higher rates of heart failure hospitalization or death.²⁰ More complete and sustained TR reduction theoretically with TTVR may provide important advantages over repair, particularly in more advanced disease when repair might not afford complete or near-complete TR reduction, although the effects of more complete TR elimination in the setting of moderate or severe RV dysfunction will require confirmation of benefit.

Several TTVR devices are in various stages of development or clinical study. The Edwards Evoque system is being studied in the TRISCEND II pivotal trial (Edwards EVOQUE Tricuspid Valve Replacement: Investigation of Safety and Clinical Efficacy after Replacement of Tricuspid Valve with Transcatheter Device) (NCT04482062) (Figure 31.2). The single-arm prospective multicenter TRISCEND study, 56 patients with a mean age of 79 years underwent TTVR with the Edwards Evoque transfemoral system with a composite major adverse event rate of 26.8% at 30 days with one cardiovascular death and significant improvements in NYHA classification and quality of life noted.²⁵ The Medtronic Intrepid Valve system is being evaluated for TTVR as well (NCT0443065). The LuX Valve (Ningbo Jencare Biotechnology Co.) underwent an initial experience after implantation in 12 patients under compassionate use and demonstrated acceptable safety and feasibility at 30 days.²⁶ The safety and feasibility of the NaviGate Cardiac

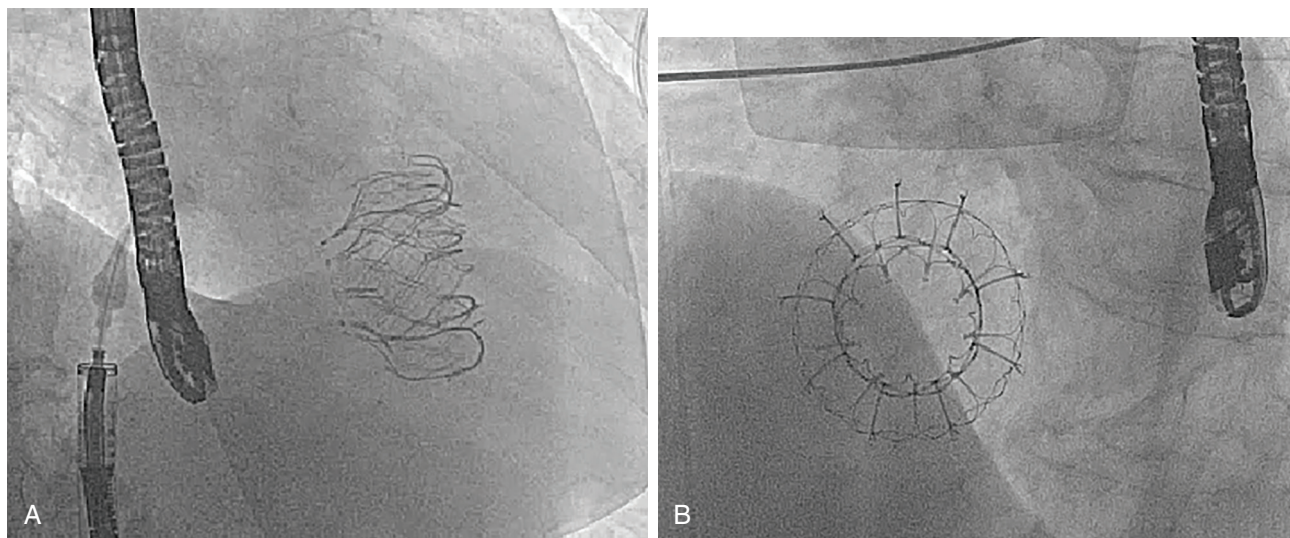


FIGURE 31.2 Transcatheter tricuspid valve replacement with the Edwards Evoque transcatheter prosthesis: side (A) and short-axis (B) views.

Structures NaviGate valved-stent procedure was demonstrated in first-in-human study in two patients considered prohibitive risk for surgery.²⁷ Other valves including the Trisol System are in early feasibility study (NCT04905017). What remains unclear about TTVR at this time are the long-term anticoagulation requirements, durability of TR reduction, and procedural safety versus valve repair techniques.

CONCLUSION

There has been a rapid advancement in the field for the treatment of severe TR because this represents an important unmet clinical need for patients. Although initial experiences are encouraging, there is much to still learn about TTVI, including timing of intervention. Only time and further study will help us to better understand how to move forward.

REFERENCES

- Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (The Framingham Heart Study). *Am J Cardiol*. 1999;83(6):897-902.
- Ebrille E, Chang JD, Zimetbaum PJ. Tricuspid valve dysfunction caused by right ventricular leads. *Card Electrophysiol Clin*. 2018;10(3):447-452.
- Park S-J, Gentry JL, Varma N, et al. Transvenous extraction of pacemaker and defibrillator leads and the risk of tricuspid valve regurgitation. *JACC Clin Electrophysiol*. 2018;4:1421-1428.
- Wang N, Fulcher J, Abeyesuriya N, et al. Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis. *Eur Heart J*. 2019;40:476-484.
- Benfari G, Antoine C, Miller WL, et al. Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction. *Circulation*. 2019;140:196-206.
- Bartko PE, Arfsten H, Frey MK, et al. Natural history of functional tricuspid regurgitation: implications of quantitative doppler assessment. *JACC Cardiovasc Imaging*. 2019;12:389-397.
- Kilic A, Saha-Chaudhuri P, Rankin JS, Conte JV. Trends and outcomes of tricuspid valve surgery in North America: an analysis of more than 50,000 patients from the Society of Thoracic Surgeons database. *Ann Thorac Surg*. 2013;96(5):1546-1552.
- Zack CJ, Fender EA, Chandrashekar P, et al. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol*. 2017;70:2953-2960.
- Moraca RJ, Moon MR, Lawton JS, et al. Outcomes of tricuspid valve repair and replacement: a propensity analysis. *Ann Thorac Surg*. 2009;87(1):83-88.
- Ratnatunga CP, Edwards MB, Dore CJ, Taylor KM. Tricuspid valve replacement: UK Heart Valve Registry mid-term results comparing mechanical and biological prostheses. *Ann Thorac Surg*. 1998;66(6):1940-1947.
- Hamandi M, Smith RL, Ryan WH, et al. Outcomes of isolated tricuspid valve surgery have improved in the modern era. *Ann Thorac Surg*. 2019;108(1):11-15.
- Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2021;77:e25-e197.
- Dreyfus GD, Martin RP, Chan KMJ, et al. Functional tricuspid regurgitation: a need to revise our understanding. *J Am Coll Cardiol*. 2015;65:2331-2336.
- Chikwe J, Itagaki S, Anyanwu A, Adams DH. Impact of concomitant tricuspid annuloplasty on tricuspid regurgitation, right ventricular function, and pulmonary artery hypertension after repair of mitral valve prolapse. *J Am Coll Cardiol*. 2015;65(18):1931-1938.
- Chorin E, Rozenbaum Z, Topilsky Y, et al. Tricuspid regurgitation and long-term clinical outcomes. *Eur Heart J Cardiovasc Imaging*. 2020;21(2):157-165.
- Topilsky Y, Khanna A, Le Tourneau T, et al. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. *Circ Cardiovasc Imaging*. 2012;5:314-323.
- Alqahtani F, Berzingi CO, Aljohani S, et al. Contemporary trends in the use and outcomes of surgical treatment of tricuspid regurgitation. *J Am Heart Assoc*. 2017;6(12):e007597.
- Wong W-K, Chen S-W, Chou A-H, et al. Late outcomes of valve repair versus replacement in isolated and concomitant tricuspid valve surgery: a nationwide cohort study. *J Am Heart Assoc*. 2020;9:e015637.
- Lurz P, von Bardeleben RS, Weber M, et al. Transcatheter edge-to-edge repair for treatment of tricuspid regurgitation. *J Am Coll Cardiol*. 2021;77:229-239.
- Mehr M, Taramasso M, Besler C, et al. 1-year outcomes after edge-to-edge valve repair for symptomatic tricuspid regurgitation: results from the Tri-Valve registry. *JACC Cardiovasc Interv*. 2019;12(15):1451-1461.
- Nickenig G, Weber M, Schueler R, et al. 6-month outcomes of tricuspid valve reconstruction for patients with severe tricuspid regurgitation. *J Am Coll Cardiol*. 2019;73:1905-1915.
- Hahn RT, Meduri CU, Davidson CJ, et al. Early feasibility study of a transcatheter tricuspid valve annuloplasty: SCOUT trial 30-day results. *J Am Coll Cardiol*. 2017;69(14):1795-1806.
- Rogers JH, Boyd WD, Bolling SF. Tricuspid annuloplasty with the Millipede ring. *Prog Cardiovasc Dis*. 2019;62:486-487.
- Asmarats L, Perlman G, Praz F, et al. Long-term outcomes of the FORMA transcatheter tricuspid valve repair system for the treatment of severe tricuspid regurgitation: insights from the first-in-human experience. *JACC Cardiovasc Interv*. 2019;12(15):1438-1447.
- Kodali S, Hahn RT, Davidson CJ, et al. Transfemoral tricuspid valve replacement in patients with tricuspid regurgitation: TRISCEND study 30-day results. *JACC Cardiovasc Interv*. 2022;15(5):471-480.
- Lu F-L, Ma Y, An Z, et al. First-in-man experience of transcatheter tricuspid valve replacement with LuX-Valve in high-risk tricuspid regurgitation patients. *JACC Cardiovasc Interv*. 2020;13(13):1614-1616.
- Navia JL, Kapadia S, Elgharably H, et al. First-in-human implantations of the NaviGate bioprosthesis in a severely dilated tricuspid annulus and in a failed tricuspid annuloplasty ring. *Circ Cardiovasc Interv*. 2017;10:e005840.



32

Hypertrophic Cardiomyopathy

SHIKHAR AGARWAL AND E. MURAT TUZCU

INTRODUCTION AND EPIDEMIOLOGY, 577

HALLMARKS AND DIFFERENTIAL
DIAGNOSIS, 577NATURAL COURSE OF DISEASE AND
CLINICAL PRESENTATION, 578

PATHOPHYSIOLOGY, 578

Left Ventricular Outflow Tract Obstruction, 578

Diastolic Dysfunction, 580

Myocardial Ischemia, 580

Autonomic Dysfunction, 580

Mitral Regurgitation, 581

Myocardial Fibrosis, 582

DIAGNOSIS, 582

Echocardiography, 582

Electrocardiography, 583

Exercise Stress Testing, 583

Cardiac Magnetic Resonance Imaging, 583

Invasive Hemodynamic Assessment, 583

MANAGEMENT OF HYPERTROPHIC
CARDIOMYOPATHY, 585

Asymptomatic Patients, 585

Symptomatic Patients, 585

NOVEL TECHNIQUES FOR SEPTAL
REDUCTION USING NONALCOHOL
SUBSTANCES, 593

SHARED DECISION MAKING, 593

HYPERTROPHIC CARDIOMYOPATHY
CENTERS, 593

INTRODUCTION AND EPIDEMIOLOGY

Hypertrophic cardiomyopathy (HCM) is a complex cardiac disorder that has been the subject of intense scrutiny and scientific investigation for the past half century. HCM is a unique cardiac condition that has the potential to manifest during any phase of life, from infancy to the ninth decade. Left ventricular outflow tract obstruction (LVOTO) is frequently, but not always, the pivotal factor in the development of symptomatic disease. Septal reduction therapy (SRT) which consists of septal myectomy (SM) or transcatheter treatment by alcohol septal ablation (ASA). The operators who carry out these procedures consistently deliver high-quality outcomes by specializing not only in the specific procedure but also having an in-depth understanding of the entire spectrum of HCM and its diagnostic and therapeutic challenges.

Since its first description in 1958,¹ HCM has been referred to by a wide variety of names, reflecting lapses in understanding of this complex disease and its clinical heterogeneity. Terms such *idiopathic hypertrophic subaortic stenosis* and *hypertrophic obstructive cardiomyopathy* are misleading because they encompass only a subset of patients who have LVOTO. In fact, roughly three-fourths of the patients have no LVOT gradient (LVOTG) at rest, and one-third of these patients do not demonstrate any LVOTG not only at rest but also with provocative maneuvers.² Accordingly, *HCM* is a more appropriate descriptive term that encompasses the heterogeneous spectrum of this disease.

Hypertrophic cardiomyopathy is a global disease and is the most common genetic cardiovascular disease encountered. The current prevalence of HCM in the adult population has been estimated to be (1 per 200 to 1 per 500 adults),^{3,4} with similar estimates for other parts of the world. In the United States, symptomatic hypertrophy is estimated to be 1 per 3000 based on administrative data.⁵ In one study, patients with HCM constituted no more than 1% of outpatients in a routine cardiology practice, implying that a substantial portion of the HCM burden remains

undiagnosed.⁶ Because of the relatively infrequent prevalence of patients with HCM, most outpatient cardiologists care for only a few patients with HCM and may not be aware of the contemporary management of this complex disease. This has led to an impetus for establishment of clinical programs of excellence, called “HCM Centers,” which would be staffed with cardiologists and cardiac surgeons familiar with the contemporary diagnostic and treatment options for HCM. These should include comprehensive history and physical examination, transthoracic echocardiography (TTE), cardiac magnetic resonance (CMR) imaging, expertise in SM, ASA, management of HCM-related arrhythmias, and heart failure as well as genetic testing and counseling.

HALLMARKS AND DIFFERENTIAL DIAGNOSIS

Hypertrophic cardiomyopathy has been defined as a disease characterized by unexplained left ventricular hypertrophy (LVH) without chamber dilatation in the absence of another cardiac or systemic disease that can produce hypertrophy, with the caveat that patients who are genotypically positive may be phenotypically negative without manifest LVH. HCM is usually recognized by a maximal septal thickness of 15 mm or greater, particularly in the presence of other compelling information such as a family history of HCM. A left ventricular (LV) septal thickness of 13 to 14 mm is considered of borderline significance. Most of the current literature has quantified LV septal thickness using echocardiography. In cases in which it is the first-line diagnostic modality, TTE is inconclusive for diagnosis and for differentiating from other pathologies and is inadequate for risk stratification and for providing accurate guidance for SRT; therefore, CMR may be used as an effective complementary imaging modality.⁷

The most common differential diagnoses of HCM include hypertensive heart disease and the physiologic remodeling of the heart seen among athletes (athlete's heart).⁸

Mild morphologic expressions of HCM or borderline HCM may be difficult to differentiate from these entities. In older individuals, HCM may coexist with hypertensive heart disease, which may pose a diagnostic challenge. The likelihood of HCM increases when the presentation is associated with a diagnostic sarcomere mutation or inferred by marked LV thickness (>25 mm) or LVOTO with systolic anterior motion (SAM) of the anterior mitral leaflet. The important distinction between pathologic LVH seen in HCM and physiologic LVH seen among athletes is the fact that the latter is usually associated with chamber enlargement; frequently, both the left ventricle and right ventricles are enlarged. Hypertrophy generally regresses when the high-level exercise routine is stopped. Besides ventricular dimensions, a detailed review of the family history, sarcomeric mutations, diastolic function, and pattern of LVH may aid in the differential diagnosis.

Several metabolic and infiltrative diseases, including various storage diseases; some congenital anomalies such as Noonan syndrome; and some other genetic disorders may mimic HCM among babies, older children, and young adults.

NATURAL COURSE OF DISEASE AND CLINICAL PRESENTATION

The understanding of the natural history of HCM has been hampered by a significant selection bias in the published literature. Early studies from the tertiary and quaternary centers reported a high annual mortality rate of 3% to 6%.⁴ With enhanced diagnostic capabilities and timely intervention using contemporary therapeutic strategies, an annual mortality rate of 1% or less is achievable in HCM centers of excellence.⁹ Patients who have high-risk features and those who have multiple comorbidities may have a higher annual mortality rate.⁴ When mortality rates are reviewed, it is important to take into consideration the population that constitutes the denominator.

The clinical course of HCM is variable and unpredictable. Although there are currently no therapies that prevent progression of this disease, most affected individuals attain normal life expectancy without any disability or need for invasive therapeutic interventions. On the other hand, when progression occurs, HCM may result in serious complications. In patients who do become symptomatic, one or more of three clinical presentations are frequently observed.

- Sudden cardiac death (SCD) caused by unpredictable and often refractory ventricular tachyarrhythmias is the most feared initial presentation. This is encountered more frequently in young asymptomatic individuals (younger than 35 years of age), including competitive athletes with HCM. Although SCD may be the first and only presentation, in some patients, syncope may be the first presentation, which should be regarded as a risk factor for SCD.
- Heart failure with or without angina results in progressively worsening exertional dyspnea. The earlier stages are characterized by diastolic heart failure without loss of systolic function. If left untreated, it may progress to

the end stage with LV remodeling and systolic dysfunction secondary to extensive myocardial scarring.

- Supraventricular tachycardia including atrial fibrillation (AF), which may be paroxysmal or permanent leads to an increased risk of systemic thromboembolism including stroke. AF with rapid ventricular response may result in abrupt decompensation of an otherwise asymptomatic patient.

In the current era, the natural history of HCM can be drastically altered by a number of therapeutic interventions, including implantable cardioverter defibrillator (ICD) implantation for prevention of SCD, medical therapy for managing heart failure symptoms, SRT for progressive LVOTO, antiarrhythmic or ablation therapies for management of AF, and last heart transplantation for end-stage HCM with refractory symptoms and severe systolic dysfunction.

PATHOPHYSIOLOGY

The pathophysiology of HCM is complex and involves an interplay of multiple factors. It is important to understand and quantify the contribution of each of the following mechanisms to an individual patient's phenotype because the management strategies are largely dependent on these pathophysiologic mechanisms.

Left Ventricular Outflow Tract Obstruction

In patients with HCM, LVOTO at rest has been demonstrated to be a strong, independent predictor of progression to severe symptoms of heart failure and death.¹⁰ In HCM, the peak instantaneous gradient rather than the mean gradient holds greater prognostic significance and influences treatment decisions. Based on the extent of LVOTO, the HCM can be divided into three groups. The patients in the first group includes those who have LVOTO (defined as LVOTG ≥ 30 mm Hg) at resting conditions. The second group includes those who have no or minimal resting gradient but develop LVOTO in response to provocation (defined as LVOTG <30 mm Hg at rest and ≥ 30 mm Hg with physiologic provocation).² The final group includes those who have nonobstructive HCM, with LVOTG less than 30 mm Hg at rest and with provocation. Marked gradients (≥ 50 mm Hg) at rest or with provocative maneuvers represent the conventional threshold for invasive management if symptoms are not controlled with medical therapy alone.

Left ventricular outflow tract obstruction in HCM is classically dynamic. In the early invasive hemodynamic studies, it was noted to vary with the loading conditions of the ventricle.¹¹ Increased myocardial contractility, decreased ventricular volume, or decreased afterload increases the severity of LVOTO. Patients with low LVOTGs at rest may generate marked obstruction with exercise, Valsalva maneuver, or with pharmacologic provocation with amyl nitrite¹² (Figure 32.1). There may be a large variation in the degree of LVOTO based on day-to-day activities, even minute to minute, based on heart rate and blood pressure or even with food or alcohol intake; exacerbation of symptoms during the postprandial period is common.¹³

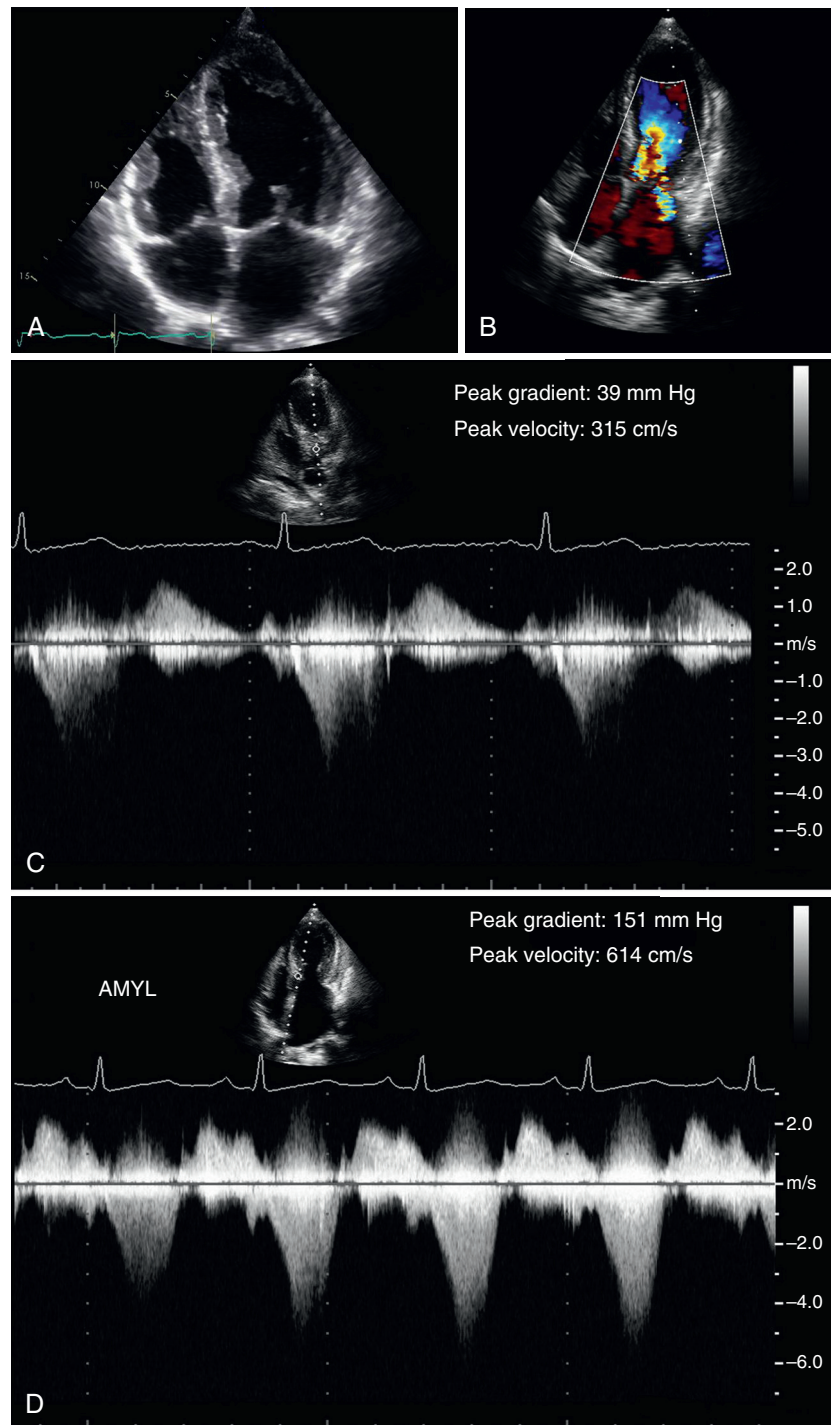


FIGURE 32.1 Measurement of left ventricular outflow tract (LVOT) gradient using continuous-wave Doppler. **A**, Apical four-chamber view of the heart showing significant upper septal hypertrophy. **B**, Color Doppler imaging showing flow acceleration across the LVOT and posteriorly directed jet of mitral regurgitation. **C**, Measurement of resting peak gradient across the LVOT of 39 mm Hg. Upon administration of amyl nitrite (AMYL), the peak gradient across the LVOT was measured to be 151 mm Hg, as seen in **D**.

Left ventricular outflow tract obstruction leads to an increase in LV systolic pressure, which leads to prolongation of ventricular relaxation, elevation of LV end-diastolic pressure, worsening mitral regurgitation (MR), myocardial ischemia, and a decrease in cardiac output. Although it was initially believed that LVOTO primarily results from the systolic contraction of the hypertrophied basal ventricular septum encroaching on the LVOT, later studies have demonstrated a greater involvement of the mitral

valve leaflets creating LVOTO by virtue of SAM of the anterior mitral leaflet and resultant mitral septal contact (Figure 32.2). Ventricular systole in HCM causes an abnormal drag force on anterior mitral leaflet that “sucks in” it into the LVOT, causing obstruction. In some patients, abnormalities of the mitral apparatus such as elongated leaflets, displacement of papillary muscles, or anomalous papillary muscle insertion into the anterior mitral leaflet may contribute to LVOTO.¹⁴

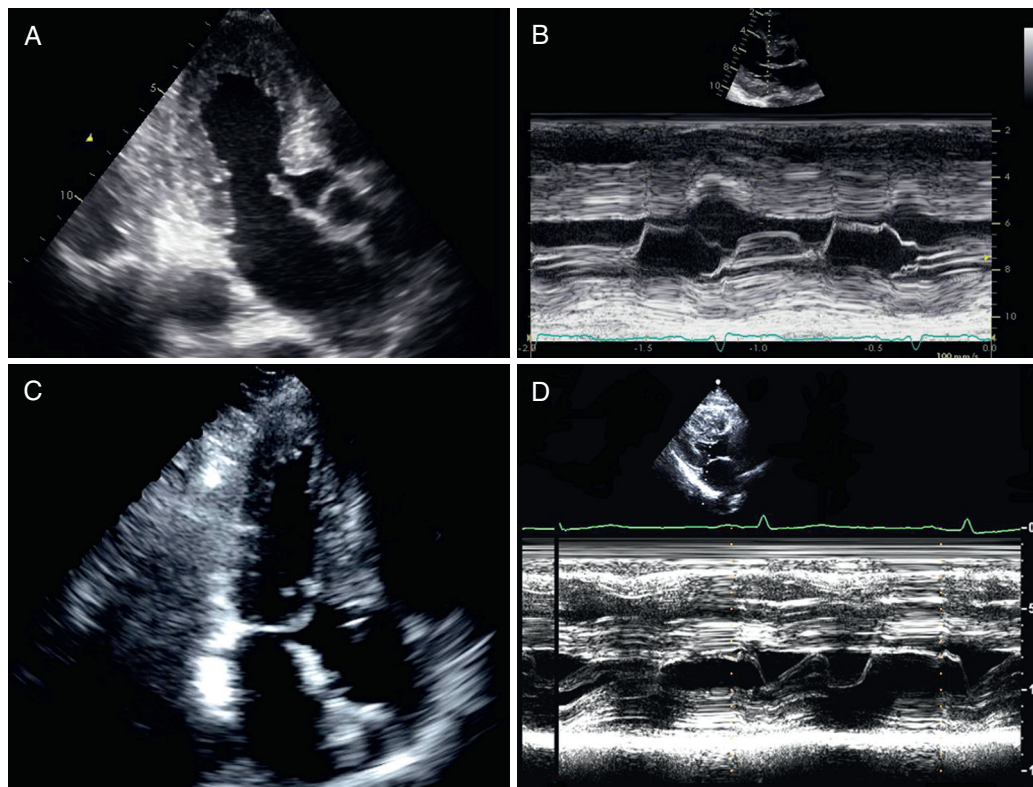


FIGURE 32.2 Systolic anterior motion (SAM) of the anterior mitral leaflet causing significant obstruction across the left ventricular outflow tract (LVOT). **A** and **B**, The apical long-axis view and the M-mode view through the mitral valve leaflets in a patient with mild SAM. There is anterior motion of the mitral leaflet that can be clearly appreciated in **B**. **C**, The apical long-axis view and the M-mode view through the mitral valve leaflets in a patient with severe SAM. There is an anterior motion of the mitral leaflet during systole with overt mitral-septal contact, which can be clearly seen in **D**.

The presence and degree of LVOTO are assessed by using two-dimensional echocardiography and continuous-wave Doppler assessment (see [Figure 32.1](#)). The peak instantaneous gradient derived from the late-peaking systolic velocity is what reflects the subaortic obstruction. If the resting outflow gradient is less than 50 mm Hg, provocative measures are used to ascertain if higher gradients can be obtained. In equivocal cases, in which there is a considerable discordance between clinical presentation and echocardiography data, invasive hemodynamic evaluation with isoproterenol infusion may further aid in eliciting a provokable gradient.¹⁵

Diastolic Dysfunction

Diastolic dysfunction is a major pathophysiologic mechanism in HCM that results in impairment of ventricular relaxation and chamber stiffness. The former results from systolic contraction against an obstructed LVOT, nonuniformity of ventricular contraction and relaxation, and a delayed inactivation caused by abnormal intracellular calcium reuptake. A marked increase in LV wall thickness results in both impaired ventricular relaxation and increased chamber stiffness. Diffuse myocardial ischemia also potentiates the amount of diastolic dysfunction encountered in HCM. With exercise, there is a decrease in diastolic filling time and an increase in the amount of myocardial ischemia, which results in worsening of the diastolic dysfunction and may cause an increase in the pulmonary capillary wedge pressure, resulting in dyspnea.

Myocardial Ischemia

Chest pain, both typical and atypical, is reported by roughly 80% of patients with HCM.¹⁶ In many cases, coronary angiography reveals normal coronary arteries. Despite this observation, several studies with functional assessment of ischemia using single-photon emission computed tomography, positron emission tomography, and CMR have demonstrated significant reversible and irreversible myocardial perfusion defects in patients with HCM.¹⁶⁻²⁰ Autopsy data have reported that up to 15% of patients with HCM may have findings of myocardial infarction (MI), which may or may not be the cause of death. This discordance suggests that microvascular dysfunction may play an important role in the development of myocardial ischemia in these patients. Microvascular dysfunction may be partly caused by arteriolar medial hypertrophy, resulting in reduced luminal diameter as well as impaired coronary vasodilatory response.²¹ The cause of myocardial ischemia is multifactorial; a demand-supply mismatch that is created by markedly thickened ventricle along with adverse loading conditions caused by LVOTO also contributes to the myocardial ischemia.

Autonomic Dysfunction

About a quarter of patients with HCM undergoing exercise stress testing demonstrate an abnormal blood pressure response to exercise characterized by a failure of systolic blood pressure to increase by at least 20 mm Hg at peak exercise or a decrease in systolic blood pressure.^{22,23} This

subset of patients has been shown to have poorer prognosis compared with those who have normal blood pressure responses.^{23,24} In addition to the potentiation of the dynamic LVOTG, it is speculated that autonomic dysregulation with resultant systemic vasodilation plays an important role in this phenomenon. It is believed that autonomic dysregulation is present in these patients, and the decrease in blood pressure and associated bradycardia may be an abnormal reflex response secondary to LVOTO.

Mitral Regurgitation

Mitral regurgitation is common in patients with HCM and may play a primary role in mediating the symptoms of dyspnea (Figure 32.3). The detailed mechanistic studies and the resolution of MR with SRT suggest that MR is frequently a secondary phenomenon.²⁵⁻²⁷ However, abnormalities of mitral valve apparatus such as elongated leaflets and displacement and insertion abnormalities of papillary muscles are also common in patients with HCM.

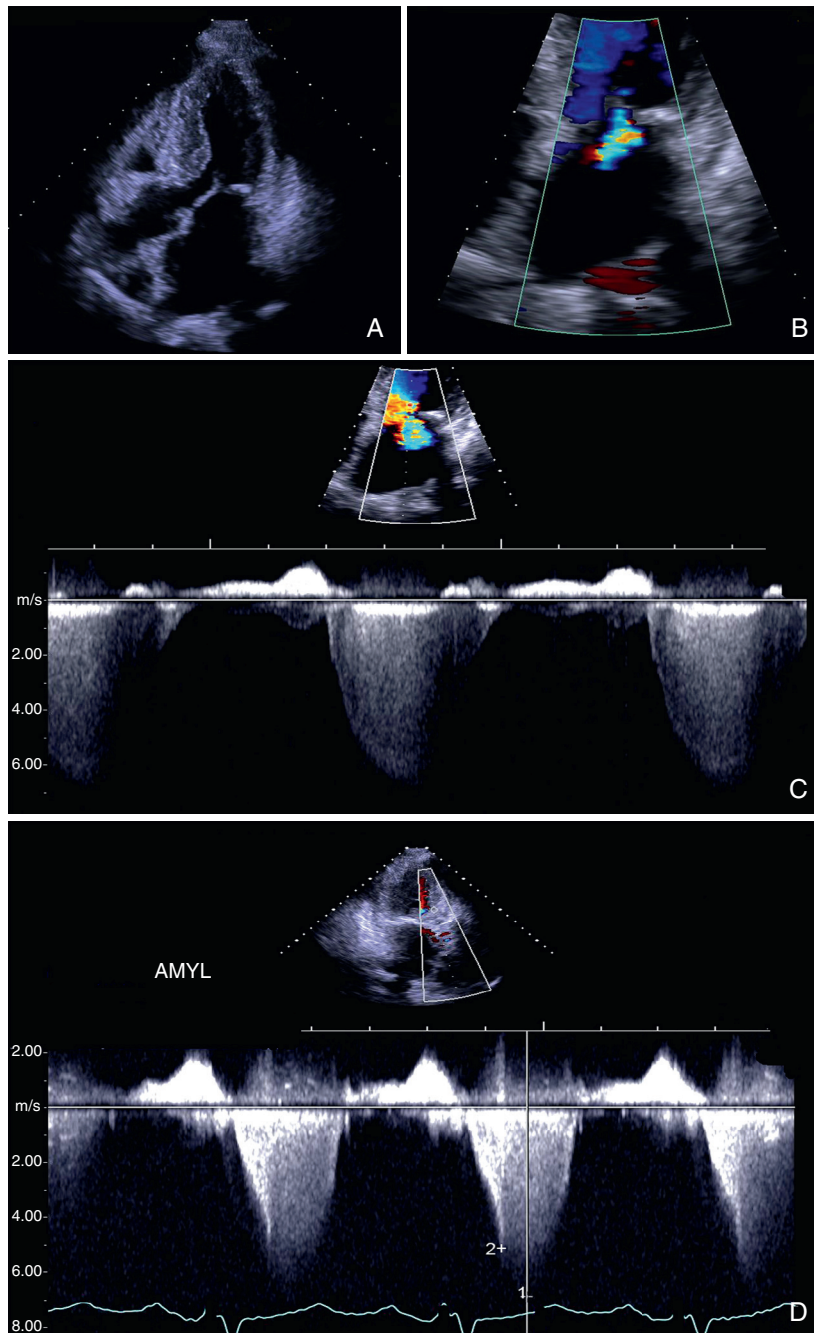


FIGURE 32.3 The importance of precise assessment of the left ventricular outflow tract gradient (LVOT) in the presence of severe mitral regurgitation (MR) is demonstrated. It is important not to misinterpret the Doppler spectral display of MR for LVOT velocities given their close spatial orientations. **A**, Apical view of the heart demonstrating significant upper septal hypertrophy. **B**, Color Doppler imaging showing flow acceleration across the LVOT and posteriorly directed jet of MR. **C**, Continuous-wave Doppler across the mitral valve to trace the Doppler spectral display of the MR jet. **D**, The Doppler spectral display of the LVOT velocities. Notice that it is contaminated by the MR Doppler display because the two envelopes appear very similar to each other. The velocity labeled 1 (614 cm/s) represents the peak MR jet velocity and would erroneously overestimate the LVOT gradient. The actual LVOT velocity in this case is represented by velocity labeled 2 (420 cm/s), which is the peak of the early dense spectral display that overlies the MR spectral display. AMYL, Amyl nitrite.

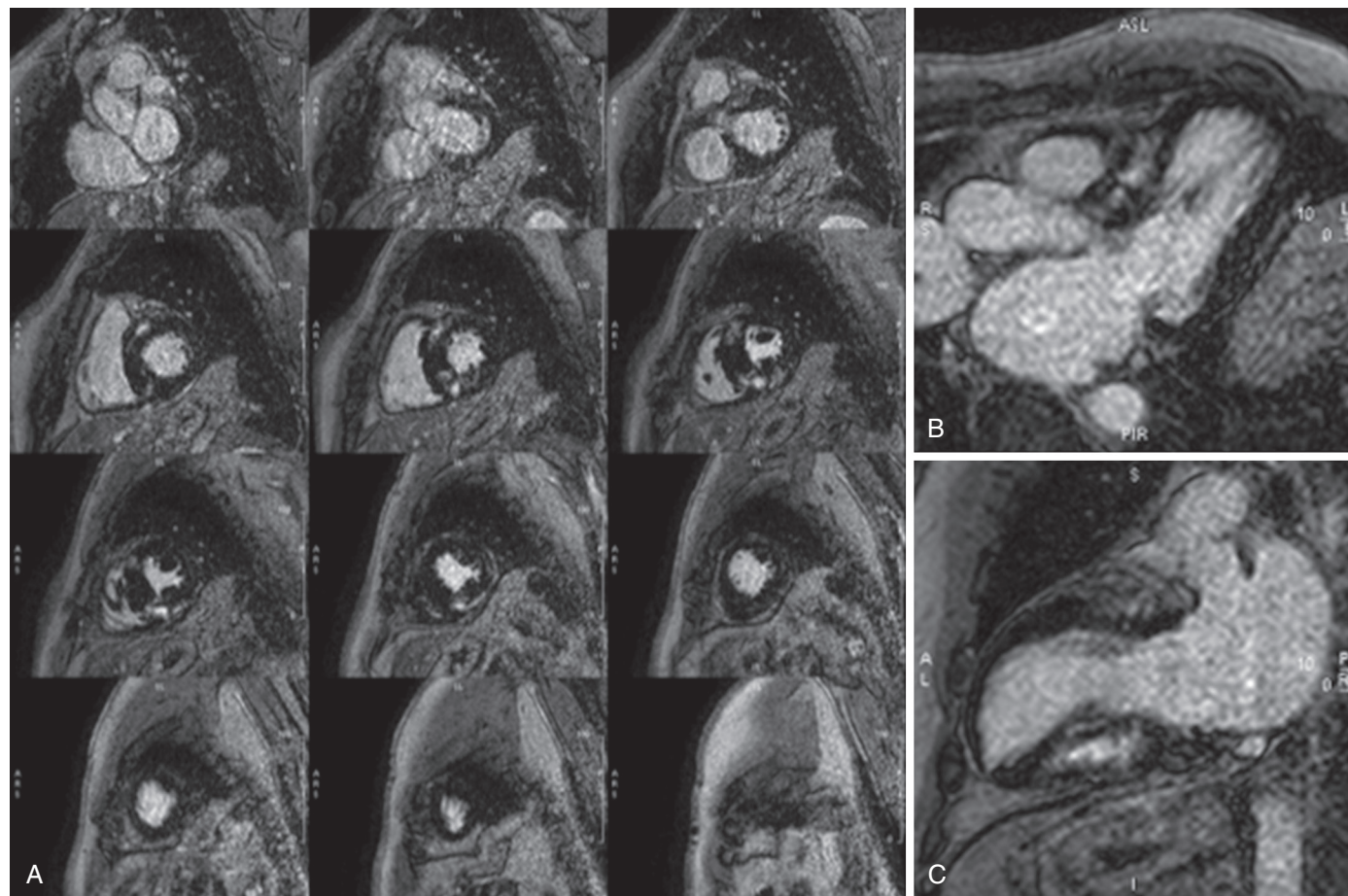


FIGURE 32.4 Cardiac magnetic resonance imaging with late gadolinium enhancement (LGE) indicative of extensive myocardial fibrosis. The *left-sided panels (A)* demonstrate consecutive short-axis images of the heart; the *upper right panel (B)* demonstrates a four-chamber representation; and the *lower right panel (C)* demonstrates a two-chamber representation. Collective interpretation of these images demonstrates a significant amount of scar involving the upper septum and inferior walls of the heart.

MR is usually caused by distortion of mitral valve apparatus from SAM-induced drag forces. In this case, the jet of MR is generally directed posterolaterally²⁸(see [Figure 32.3](#)). An anterior or anteromedially directed jet should suggest an intrinsic abnormality of the mitral valve apparatus. However, caution is warranted not to rely on jet direction for definitive diagnosis. If the mechanism of MR is directly related to SAM, changes in ventricular load and contractility would affect the degree of MR as well as LVOTO. It is very important to identify patients with intrinsic abnormality of mitral valve such as prolapse or flail leaflets. Such findings have major implication on the planning of SRT. It is important to note that operators of SRT should be very familiar with the echocardiographic examination of patients with HCM to choose the right procedure(s).

Myocardial Fibrosis

Histopathologic examination of myocardium affected by HCM typically demonstrates myocardial fiber disarray with markedly thickened cardiomyocytes arranged in whirls and branches and an increased amount of fibrosis, especially in advanced cases. It may be speculated that this cellular disarray reduces the contractile force of the affected myocardium, which in turn stimulates the

hypertrophic process. CMR is considered to be the best tool for identification and quantification of myocardial fibrosis. The presence of fibrosis is suggested by late gadolinium enhancement (LGE) of affected myocardium. ([Figure 32.4](#)). LGE imaging detects accumulation of contrast in areas of fibrosis because of slower contrast kinetics and greater volume of distribution in the extracellular matrix. LGE quantification is used in the risk stratification for sudden death. Tissue Doppler imaging and speckle tracking can also help determine the extent of fibrosis in HCM. Low septal tissue velocity (<5 cm/s; normal >8 cm/s) corresponds to increased early diastolic stiffness of the fibrotic septum ([Figure 32.5](#)).

DIAGNOSIS

Echocardiography

In addition to a detailed history and through physical examination, several tests are used to decide on the most appropriate management of patients with HCM. Foremost among these tests is TTE, which is the most common method for establishing the clinical diagnosis of HCM via identification of a thickened nondilated left ventricle in the absence of other comorbidities known to cause LVH.

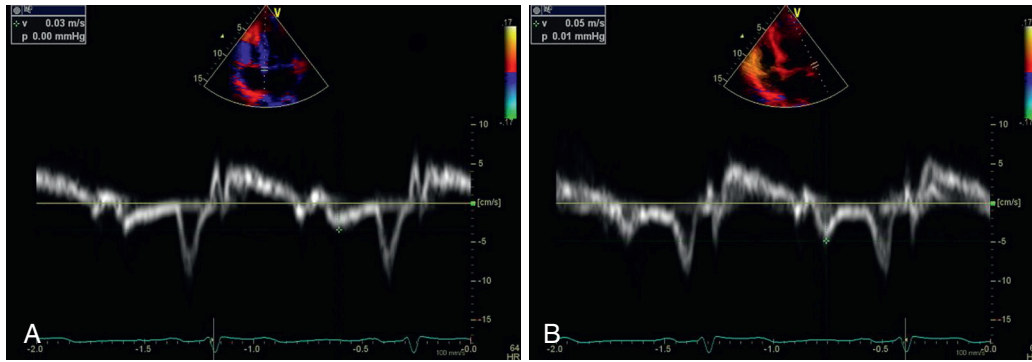


FIGURE 32.5 Tissue Doppler imaging in a patient with hypertrophic cardiomyopathy. **A**, Markedly low early diastolic tissue velocities at the level of medial mitral valve annulus (3 cm/s). **B**, Markedly low early diastolic tissue velocities at the level of lateral mitral valve annulus (5 cm/s).

Although classically thought to involve the upper septum, HCM can result in any pattern of LV thickening.²⁹ Quantifying the extent and thickness of the septal hypertrophy, systematic review of the morphologic as well as functional aspects of mitral valve apparatus, ventricular and atrial size and function, and determination of valvular and other structural cardiac abnormalities can be accomplished by a careful echocardiographic examination. Determining the severity of MR and its mechanism requires meticulous attention to the structural and functional abnormalities in the entire heart. Preprocedural assessment of the diastolic function of the left ventricle is important in the assessment of the postprocedure course of the patient. Echocardiography has a pivotal role during the SRT. In the surgical suite, transesophageal echocardiography (TEE) guides the surgeon to achieve resolution of the LVOTG and MR.³⁰ Echocardiography also plays a critical role during ASA. Choosing the septal perforator branch that supplies the targeted septal area is done by TTE imaging after intrabranched echo contrast injection. The ability to monitor the LVOTG in response to alcohol injection allows the optimization of procedural outcomes.^{31,32}

Electrocardiography

Careful examination of the baseline electrocardiogram is essential in estimating the risk during the patient's postprocedure course. Those with baseline conduction abnormalities may be at high risk for procedure-related heart blocks requiring a permanent pacemaker. The presence of right and left branch block increase the risk for complete heart block after SM and ASA, respectively. Preprocedural evaluation should also include 4-hour ambulatory ECG monitoring recommended by the current American College of Cardiology/American Heart Association (ACC/AHA) guidelines (Class I) helps in risk stratification and in planning of postprocedural management of the patient.⁷

Exercise Stress Testing

Stress echocardiography provides valuable information, including exercise capacity, worsening symptoms, LVOTO and MR in response to exertion, exercise-induced arrhythmias, hemodynamic changes with exertion, and other high-risk characteristics such as marked ECG changes or

hypotension during exercise.^{23,33} These data points are essential for risk stratification and management decisions. Improvement in functional capacity after SRT can be evaluated with postprocedure exercise tests. Performing cardiopulmonary stress testing by simultaneously analyzing the respiratory gases provides more specific information about the patient's functional capacity.³⁴

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging offers multiple advantages to better detect areas of LVH that are not well visualized or missed by TTE. These include superior resolution with precise morphologic characterization, enhanced tissue contrast capability, and production of three-dimensional images. The current ACC/AHA guidelines recommend CMR for patients with suspected HCM when echocardiography is inconclusive or equivocal for establishing diagnosis (Class I).⁷ In many centers, CMR is used routinely in the evaluation of patients with HCM, particularly in those who are considered for SRT in whom additional information about magnitude and distribution of hypertrophy or anatomy of the mitral valve apparatus or papillary muscles are needed.⁷

Contrast-enhanced CMR allows identification and quantification of myocardial fibrosis based on areas of myocardium with LGE (see Figure 32.4). In a prospective cohort study, extensive LGE was found to be an independent predictor of sudden death. However, the independent predictive value of LGE is still debated among experts. Current ACC/AHA guidelines recommend CMR as a complementary imaging modality.⁷ Recent reports highlight the heterogeneous natural history of myocardial fibrosis documented by change in extent of LGE. In a two-center North American study, progression of LGE was significantly correlated with a number of clinical outcomes such as worsening LV function and heart failure admission.³⁵ Further studies with serial imaging at predetermined intervals are needed to determine the predictive value of scar progression shown by CMR.

Invasive Hemodynamic Assessment

Given the vast amount of diagnostic and prognostic information that can be derived with noninvasive modalities

already discussed, cardiac catheterization is generally not required for the diagnosis of HCM. Invasive hemodynamic evaluation is generally used if noninvasive imaging is insufficient to qualify or quantify the degree of LVOTO.

In everyday practice, gradient measurement across the LVOT is accomplished by placement of a pigtail catheter in the aortic root and another pigtail catheter, preferably one without holes in the distal shaft, into the LV cavity. Attention should be paid to the fidelity of the pressure tracings. If there is evidence of entrapment in midcavity or inaccuracy because of recording LVOT rather than LV cavity pressure. If there is any doubt about the accuracy of the measurements, a pigtail catheter should be introduced into the LV inflow under the mitral valve via the transseptal route. When the precise location of the obstruction is in doubt, direct measurement and localization of the gradient can be performed by placing an end-hole catheter at the LV apex and then slowly withdrawing it while continuously monitoring the pressure waveform. Placing a wire in the LV apex and introducing the end-hole catheter over the wire help to perform a controlled, steady pullback and

accurate determination of the level of obstruction. Occasionally, a subaortic membrane or aortic valvular stenosis may contribute to the LV-aortic gradient more than revealed by noninvasive measurements.

Because the gradient across the LVOT is generally labile, various physiologic and pharmacologic maneuvers may be needed to accentuate the LVOTO. One of the classical signs described is the Brockenbrough-Braunwald-Morrow sign, or the post premature ventricular contraction (post-PVC) potentiation.¹¹ This refers to the augmentation of the LV pressure with a concomitant decrease in the aortic systolic and pulse pressures as a result of increased LVOTO in the cardiac cycle that follows a PVC (Figure 32.6). Post-PVC increase in the gradient between LV and aorta is seen in valvular aortic stenosis (AS), too, but unlike HCM, the pulse pressure (reflective of the stroke volume) does not decrease. This is because, in AS, a larger stroke volume of the post-PVC beat leads to a higher gradient with no change in the severity of obstruction.

In most centers, routine coronary angiography is performed for middle-aged and older adults before planned

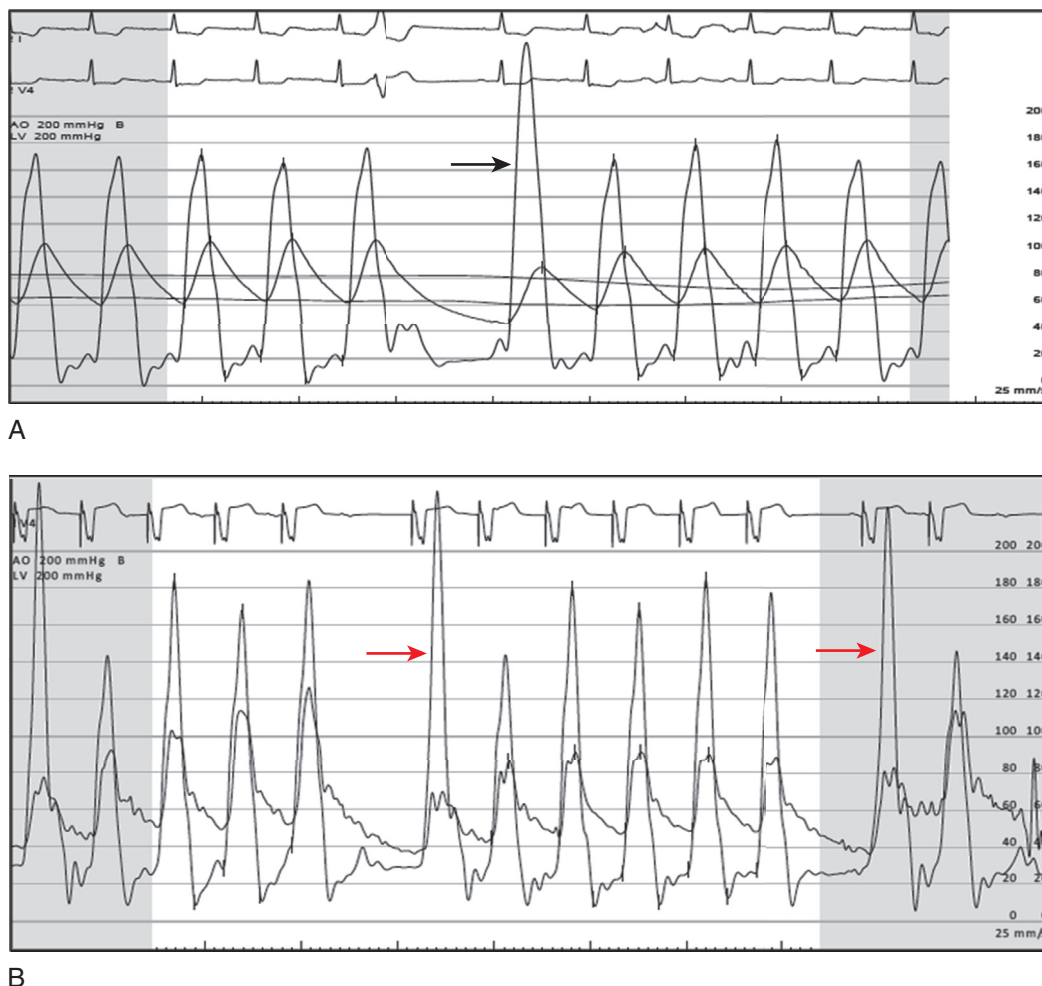


FIGURE 32.6 The Brockenbrough-Braunwald-Morrow sign. The hemodynamic tracings shown in the two panels were obtained with simultaneous measurement of left ventricular (LV) pressure waveform and aortic pressure waveform with two catheters. **A**, The classic sign with marked augmentation of the LV pressure with a concomitant decrease in the aortic systolic and pulse pressures as a result of increased left ventricular outflow tract (LVOT) obstruction in the cardiac cycle that follows a premature ventricular contraction (PVC) (black arrow). **B**, A modified version of this sign in a patient with a dual-chamber pacemaker, who was pacing in an “A-sense, V-pace” manner. It can be clearly appreciated that there are differing RR intervals secondary to irregular atrial activity. The red arrows demonstrate the beats after an unusually long RR interval. The hemodynamic tracings mimic the classic sign, with an augmentation of the LV pressure with a decrease in the aortic systolic, and pulse pressure, during beats with long RR interval.

SM. Coronary angiography should also be done in younger patients if there is angina, especially in the presence of traditional risk factors for atherosclerotic heart disease (Class I).⁷ Coronary angiography is required in the planning stage of ASA to evaluate the coronary anatomy, specifically the septal perforator branches.

Coronary arteries are generally free of obstruction in patients with HCM. Because of significant hypertrophy of the septum, compression of the septal perforator branches and occasionally of the left anterior descending coronary artery (LAD) may be seen during systole, resulting in a classically described “sawfish” appearance.³⁶ In some patients, septal perforator branches may misleadingly appear too small for ASA because of compression. Myocardial bridging (or tunneling) may be present in up to 40% of patients with HCM.³⁷ Myocardial bridging may be responsible for causing angina in the absence of significant epicardial coronary artery stenosis. Although it has been suggested that intermittent ischemia as a result of myocardial bridging could be a potential mechanism for sudden death in patients with HCM,³⁸ there has been no convincing evidence to support this hypothesis in adults or children.^{39,40} Left ventriculography may demonstrate systolic cavity obliteration, MR, and occasionally hypertrophied septum prolapsing into the LVOT. Images in left anterior oblique projection are best suited to delineate the morphology of LVOT and SAM.

MANAGEMENT OF HYPERTROPHIC CARDIOMYOPATHY

Management of patients with HCM requires a thorough understanding of the complex pathophysiology and symptomatic and hemodynamic status of the patient. Management decisions often need to be individualized to the patient based on the presence and extent of obstructive physiology, symptoms and their persistence, LV systolic function, surgical candidacy, comorbidities, and patient preferences.

Asymptomatic Patients

A large proportion of patients with HCM are asymptomatic, and a majority of them generally achieve a normal life expectancy. Risk stratification for SCD must be performed meticulously in all patients with HCM, irrespective of symptomatology. Education is key, and it is essential to counsel all patients and their families about the disease process, screening of all first-degree relatives, and avoidance of strenuous activity in competitive athletes.⁴¹ According to the current ACC/AHA guidelines, it is recommended that comorbidities that contribute to atherosclerotic disease such as hypertension, diabetes, hyperlipidemia, and obesity be aggressively treated in compliance with existing relevant guidelines (Class I).⁷ This is because concomitant coronary artery disease (CAD) has a significant adverse impact on survival in patients with HCM.⁴² A low-intensity aerobic exercise regimen is reasonable to achieve optimal cardiovascular fitness.^{7,43}

Although the usefulness of beta-blockade and calcium channel blockade to alter the natural course of disease is

not well established in asymptomatic patients, these agents may be used to treat relevant comorbidities such as hypertension (Class IIb).⁷ Some preliminary data in animal models have demonstrated the efficacy of angiotensin-converting enzyme inhibitors or statins or calcium channel blockers in halting progression of LVH.⁴⁴

Septal reduction therapy is currently not recommended for asymptomatic patients with HCM with normal exercise capacity regardless of the extent of LVOT obstruction (Class III).^{7,9,45} The indication of SRT is to improve symptoms refractory to medical therapy, resulting in significant impairment of quality of life. Therefore, they should not be performed in asymptomatic patients solely based on the extent of resting or provokable LVOTG.

Symptomatic Patients

Medical Management

Medical therapy should be used as the initial therapeutic approach for the treatment of symptomatic patients with HCM. Current pharmacotherapy for HCM is largely based on expert opinion, clinical experience, and retrospective observational analyses. Patients with LVOT obstruction constitute the largest segment of the symptomatic patients. Besides those with obstruction, a significant number of nonobstructing patients may also be symptomatic because of diastolic dysfunction, resulting in heart failure, angina, and AF, which may require treatment.

Beta-Blockers

According to the current ACC/AHA guidelines, beta-blockers should be used as primary pharmacologic therapy for treatment for symptoms in adult patients with obstructive or nonobstructive HCM. It is often useful to titrate the dose to a resting heart rate below 60 to 65 beats/min (up to generally accepted and recommended maximum doses of individual agents) (Class I).⁷ A cautious approach is warranted in patients with sinus bradycardia or severe conduction disease (Class I).⁷ Beta-blockers are effective because of their negative inotropic effects and their ability to attenuate adrenergic-induced tachycardia. These effects significantly reduce myocardial oxygen demand, thereby reducing myocardial ischemia. The reduction in resting heart rate prolongs the diastolic filling period, which allows for more efficient inactivation of myocardial contractile proteins and improving diastolic filling mechanics.^{44,46,47} Because of their negative chronotropic properties, these agents are especially helpful in patients with supraventricular tachycardia. The first agent initially used for treatment, propranolol, has largely been replaced by the newer generation, longer acting, cardioselective agents such as metoprolol, which was recently studied in a randomized trial. In the TEMPO trial, investigators randomized patients with New York Heart Association (NYHA) Class II or greater and resting or provokable LVOTG to metoprolol succinate ($n = 29$) or placebo ($n = 29$) for 2 weeks followed by a 2-week wash-out period and a 2-week cross-over period when patients received the opposite treatment.⁴⁸ Treatment with metoprolol reduced LVOT obstruction at rest (33 ± 25 mm Hg), with Valsalva maneuver (66 ± 48 mm Hg), at peak exercise (47 ± 36 mm Hg), and after exercise (71 ± 63 mm Hg). It

also improved symptoms and mildly benefitted quality of life but did not improve maximum exercise capacity, pVO_2 (pulmonary venous saturation), or diastolic function. This is an important study albeit a small one with only 2 weeks of follow-up. Further studies are needed to determine the role of beta-blockers among the emerging new specific agents.

Calcium Channel Blockers

The nondihydropyridine calcium channel blocker verapamil has been traditionally used in patients with HCM. According to the current guidelines, verapamil or diltiazem therapy is recommended for treatment of symptoms in patients with obstructive or nonobstructive HCM who do not respond to beta-blockers or who have adverse effects or contraindications to the use of beta-blockers (Class I).⁷ At the current time, there is no evidence to suggest that combination therapy with verapamil and beta-blockers is more effective than either a beta-blocker or verapamil alone. Verapamil should be used cautiously in patients with a large resting LVOTG owing to the risk of severe hemodynamic compromise, resulting in cardiogenic shock and pulmonary edema.⁷ The current guidelines recommend against the use of verapamil in patients with obstructive HCM in the setting of systemic hypotension or severe dyspnea (Class III).⁷

Nifedipine and other dihydropyridine calcium channel blockers are potentially harmful for treatment of symptoms in patients with HCM who have resting or provokable LVOTG (Class III).⁷ This is because their vasodilatory effects may exacerbate the outflow obstruction, possibly leading to worsening of current symptoms.

Disopyramide

Disopyramide has been in the armamentarium for HCM for more than 4 decades. It is a Class IA antiarrhythmic agent that also functions as a negative inotropic effect and leads to a relative increase in the systemic vascular resistance. The current ACC/AHA guidelines consider it reasonable to combine disopyramide with beta-blockers or calcium channel blockers in treatment of symptomatic obstructive HCM in patients who do not respond to beta-blockers or calcium blockers alone (Class IIa).⁷ Although it does not appear to have any effect on the diastolic dysfunction, disopyramide has been shown to effectively reduce the outflow obstruction with improved symptomatic control in patients who are refractory to other forms of therapy.⁴⁹ Patients should be monitored for proarrhythmic effects and anticholinergic side effects. The use of disopyramide alone without beta-blockers or verapamil is potentially harmful in patients with HCM with AF because disopyramide may enhance atrioventricular conduction and increase the ventricular rate during episodes of AF (Class III).⁷

Mavacamten

Mavacamten, which is a small molecule, acts by modulating β -cardiac myosin. It reduces the hypercontractility of the myocardium in HCM patients. In a multicenter trial, 251 patients with 50 mm Hg or greater were randomized to this new agent and placebo for 30 weeks.⁵⁰ The study drug improved exercise capacity, LVOTO, NYHA functional

class, and health status. Recently, detailed analysis of the serial echocardiographic studies of patients in the EXPLORER trial was reported.⁵¹ Mavacamten was shown to significantly improve LV diastolic function, left atrium wall index, and E/e' with associated reduction in N-terminal (NT)-prohormone BNP (NT-proBNP). These are promising findings for specific treatments targeting the pathophysiology underlying HCM. However, further comparative studies with longer follow-up periods are needed to make radical changes in the current treatment recommendations.

This is a major advance in a field in which no new drug was introduced for decades. However, further studies will be needed to fully understand mavacamten's incremental value and precise role in the therapeutic armamentarium for HCM given the exclusion of most severely symptomatic patients and the restrictions of the medical treatment in the placebo arm such as discontinuation of disopyramide and no dosage changes in beta-blockers and calcium channel blockers in the randomized trial.

Other Agents

In HCM, the medications not to be used or to be used cautiously is as important as those that are in the therapeutic armamentarium. It is important to avoid dehydration and environmental circumstances and medications that promote vasodilation among all asymptomatic patients with resting or provokable LVOTG. Hence, high-dose diuretics and vasodilators should be avoided in patients with HCM because they may promote a smaller LV cavity and exacerbate the degree of LVOTO and clinical picture.⁷ Intravenous (IV) phenylephrine is the only recommended agent for treatment of acute hypotension in patients with obstructive HCM who fail to respond to IV fluid administration (Class I).⁷ Use of norepinephrine, dopamine, dobutamine, or other positive inotropic agents is potentially harmful for the treatment of hypotension in patients with symptomatic HCM and is not recommended (Class III).⁷

Invasive Management

The current ACC/AHA guidelines recommend that SRT should be performed in *eligible* patients with LVOTO resulting in severe drug refractory symptoms (NYHA class III–IV) and as defined by the following core criteria:

- Clinical: severe angina or dyspnea (NYHA class III/IV) or other symptoms such as syncope or near syncope that interfere with activities of daily living or adversely affect quality of life despite adequate medical therapy
- Hemodynamic: resting or provokable LVOTG more than 50 mm Hg associated with septal hypertrophy and SAM of the mitral valve
- Anatomic: targeted septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator.

Septal reduction therapy that includes SM and ASA should not be done in patients who are asymptomatic with normal exercise tolerance or whose symptoms are controlled on optimal medical therapy (Class III).⁷ Although these are methodologically very different interventions, they have been treated under the heading of SRT in ACC/AHA guidelines as well as the current European guidelines because they are both accepted methods for relief of

symptoms in patients with LVOT obstruction.^{7,45} There are some important points in tailoring individual therapies among the affected population, which have been discussed further in this chapter. SM has been used for the past 50 years, and relief of LVOT obstruction can be achieved with low perioperative morbidity and mortality in experienced centers.^{52,53} Until relatively recently, SM was considered as the treatment of choice in most patients who meet criteria for invasive management of HCM based on the reports from small number of high-volume centers demonstrating excellent short and long-term results. However, refinements and accumulated experience resulted in improvement in safety and effectiveness of ASA. For most patients with HCM who are in need of SRT, SM and ASA offer comparable outcomes, although follow-up after ASA is not as long as after SM. Particular considerations that would favor SM include concomitant cardiac disease such as intrinsic mitral valve disease that require surgical correction and massive septal hypertrophy. Specific abnormalities of the mitral valve apparatus can contribute significantly to the generation of LVOTG, suggesting the potential value of additional surgical approaches (e.g., plication, papillary muscle relocation, valvuloplasty). ASA causes a regional infarction of the basal septum, thereby initially decrease contractility followed by gradual thinning of the basal septum and consequent widening of the LVOT. Among patients who meet core criteria for SRT, considerations that favor the use of ASA over SM include advanced age, significant noncardiac comorbidities that significantly increase surgical risk, and the patient's desire to avoid open heart surgery after a thorough discussion of both options.

Some experts proposed not limiting the SRT to only severely symptomatic patients given the safety of the SRT procedures and improvement in the quality of life in experienced centers.^{54,55} Others highlight the potential for using SRT in minimally symptomatic or asymptomatic patients with high LVOTGs considering the known unfavorable impact of severe LVOTO on prognosis and emerging data supporting early intervention to asymptomatic patients with valvular disease.⁵⁶

It has been recommended that both of these procedures should be performed after shared decision making by experienced operators in a multidisciplinary HCM center. The ACC/AHA guidelines define an experienced operator as someone with a cumulative case volume of at least 20 procedures or an individual operator who is working in a dedicated HCM program with a cumulative total of at least 50 procedures.⁷ In addition, given the data available from experienced centers, operators should aim to achieve mortality rates below 1% and major complication rates below 3%, with documented improvement in hemodynamics and symptoms of their treated HCM patients. Therefore, SRT should be performed as part of a program dedicated to the longitudinal and multidisciplinary care of patients with HCM.⁷

Septal Myectomy

Although published literature demonstrates a considerable improvement in the surgical results over the past few decades, the data are limited to a relatively few high-volume

centers with extensive experience and particular interest in the treatment of patients with HCM. There has been a significant evolution in the surgical therapy from the original isolated SM performed by Goodwin et al. in 1960⁵⁷ to the more modern, and widely used Morrow myectomy.⁵⁸ The Morrow myectomy is performed via the transaortic approach so that the proximal septum is visualized and 5 to 15 g of myocardial tissue is resected from the base of the aortic valve to a region distal to the area of the mitral-septal contact that results in enlargement of LVOT and eradication of the gradient.^{58,59} It is critically important to correctly identify the involved portion of the LV septum and resect enough myocardium to relieve the LVOTG. Intraoperative TEE is used to assist with the localization of the desired region for resection and to monitor the impact of resection on the LVOTG during surgery.

In patients with concomitant disorders such as AF or CAD, SM may be combined with adjunctive procedures such as surgical treatment for AF (MAZE) or coronary artery bypass grafting. Abnormalities of mitral valve apparatus such as elongated and flexible leaflets or insertion abnormalities of the papillary muscles may contribute substantially to the degree of LVOTO in some patients. These patients often benefit from additional surgical procedure at the time of myectomy to effectively reduce the LVOTO and decrease the associated MR.⁶⁰ Mitral valve repair is reserved for patients with significant primary valvular abnormalities such as myxomatous degeneration leading to mitral valve prolapse and severe MR. Mitral valve replacement should be considered as a last resort. The surgical specimen obtained during SM should be submitted for histopathologic examination, not only to confirm the diagnosis of HCM but also for special stains to rule out other storage disorders that can mimic HCM.⁶¹ Additionally, histopathology of the hypertrophied septum may provide clues for postablation prognosis.⁶²

PATIENT SELECTION. Septal myectomy SM can be considered in all moderately or severely symptomatic patients with obstructive HCM except in those who exhibit high surgical risk because of comorbidities. Particular considerations that lead to the choice of SM rather than ASA as SRT technique include concomitant cardiac disease that require surgical correction and massive septal thickness. SRT may be considered in selected mildly symptomatic (NYHA class II) patients who have significant hemodynamic characteristics such as severe progressive pulmonary hypertension, left atrial enlargement and paroxysmal AF, concerning ventricular arrhythmias, and markedly reduced exercise capacity.^{7,63-65}

RESULTS. Multiple observational studies have demonstrated SM alone to be a safe and effective procedure for relief of LVOT obstruction, resulting in resolution of heart failure and improvement of exercise capacity and quality of life in patients with HCM who remain significantly symptomatic on maximal tolerated pharmacologic therapy. In the most experienced centers, the mortality rate for isolated SM approaches 1% or less.^{52,66} SM together with mitral valve surgery carries still acceptable but higher risk even in high-volume centers.⁶⁰

Very low residual gradients, improvement in quality of life, and favorable remodeling of cardiac chambers and

accompanying hemodynamic stabilization are predictable results in the hands of experienced expert surgeons. Unfortunately, these levels of safety and effectiveness are reported by only a handful of surgical centers.⁶⁷

Although randomized controlled trials comparing SM with medical therapy do not exist, nonrandomized studies have demonstrated that SM resulted in excellent long-term survival similar to that in the general population.^{52,53} The rate of SCD or inappropriate ICD discharge after SM is lower, yet SM does not eliminate the need for individual SCD risk assessment and consideration of placement of ICD in those with a significant risk burden.

COMPLICATIONS. Septal myectomy is a safe procedure. In a recent study based on the US STS registry, the average risk of operative mortality after isolated SM reported to be 1.6% and major morbidity was around 10%.⁶⁰ Although left bundle branch block is relatively common after surgery, the risk of complete heart block was found in the same study as 3.7%.⁶⁰ It is higher in patients with preexisting right bundle branch block or those previously underwent ASA. In this study, the rate of iatrogenic ventricular septal defect requiring repair was 0.7%, and the rate of unplanned aortic valve replacement was 1.5%.

Alcohol Septal Ablation

First performed by Sigwart in 1995,⁶⁸ ASA was intended for symptomatic patients who do not wish to undergo invasive open-heart surgery, for those who were suboptimal surgical candidates because of comorbidities, and those who were located in areas without sufficient surgical expertise. Through the selective infusion of absolute (100%) ethanol into either the first or second septal perforator branches, the ASA technique attempts to mimic the effect of the myectomy by inducing a controlled infarction in the basal portion of the hypertrophied septum, resulting in scarring, thinning, and akinesis, leading to a significant reduction in the LVOTG and SAM of the anterior mitral valve leaflet. Since its inception, iterative technical refinements, such as meticulous attention to targeting the segment to be ablated using contrast echocardiography and angiography, minimizing amount of alcohol, and administering alcohol slowly, have led to lower complication rates and better outcomes.

PATIENT SELECTION. Alcohol septal ablation has the potential for a greater patient satisfaction because of its minimally invasive character, lack of surgical incision and general anesthesia, less overall discomfort, a much shorter recovery time, and a shorter hospital stay. It is well known that the perioperative risks and complications of cardiac surgery increase with age and therefore ASA might offer a selective advantage in older patients in whom surgical risk is high because of comorbidities. ASA is not currently indicated in children.

Although most patients can be treated with ASA, there are some caveats that should be taken into account. With the refinements in the technique of ASA, the risk of requiring permanent pacemaker implantation after ASA is lowered to 10% to 12%, but it is still significantly higher than seen after SM.⁶⁹ Higher repeat procedure rates and limited effectiveness in extremely thick septum as well as lack of surgical complications such as major bleeding, infections,

and early reoperations should be considered during patient selection for ASA.

PROCEDURAL TECHNIQUE (VIDEO 32.1). The procedure is generally performed under conscious sedation with special attention to pain control at the time of alcohol infusion into the septal perforator. The first step of the procedure is to perform a standard diagnostic coronary angiography to clearly define the coronary anatomy and evaluate for concomitant atherosclerotic disease (Figure 32.7). For the clearest anatomic characterization of the septal anatomy coursing through the basal interventricular septum, the C-arm is usually positioned in the right anterior oblique cranial or the posteroanterior (PA) cranial projections. At times, the septal anatomy may vary such that one subdivision may run along the left side of the septum while another runs along the right side. Angiography in the left anterior oblique cranial projection often helps determine the septal vessels' course along the septum (i.e., leftward or rightward). Selection of the left-sided subdivision is advised because there is a significantly less likelihood of complete heart block during ethanol infusion into the leftward branches compared with the rightward branches. Although in a majority of cases, the septal perforators arise from the LAD, substantial anatomic variation has been described in which the vessels may be seen to arise from the left main trunk, the ramus intermedius, the left circumflex, the diagonal branches, or even the branch of the right coronary artery.⁷⁰ After the image acquisition is completed, the operator should select the appropriate septal perforator branch to ablate.

After completion of diagnostic coronary angiography, a temporary transvenous pacemaker is placed as a prophylactic measure in case complete heart block develops during or after the procedure. Some operators prefer placing a screw-in active fixation lead via the right internal jugular vein. After successful placement of the sheaths and pacemaker, heparin is administered intravenously to achieve activated clotting time of 300 or greater to prevent thrombosis in the guiding catheters or wires as well as in the coronary arteries.

Several important considerations must be included in the selection of the septal perforator for ablation. Foremost, the chosen branch should be the one supplying the target myocardial territory in the upper septum. It is usually but not always the first septal perforator originating from LAD. Other considerations include vessel size, angulation, and branching of the septal perforator. Vessels with angulation greater than 90 degrees may pose technical challenges and result in frequent prolapse of the wire into the mid-LAD. In some cases, passing the balloon across the tortuous segment and securing it in place may not be easy. Technical expertise and specialized equipment may be helpful in these infrequent cases. Assessment of all myocardial territories supplied by the septal perforator is of paramount importance to avoid causing MI in unintended territories. It has been demonstrated that there is substantial variation in the perforator anatomy in patients with HCM compared with normal control participants. In both angiographic and autopsy studies, it has been demonstrated that the first septal perforator may supply regions other than the basal septum such as part of the right

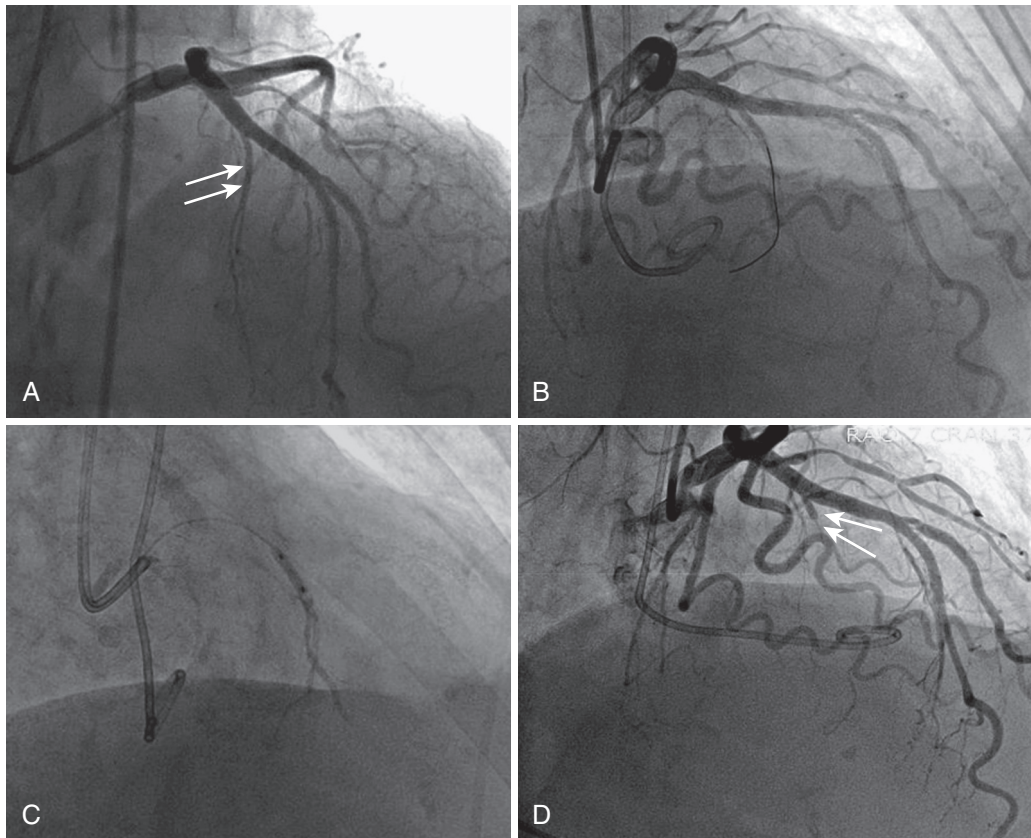


FIGURE 32.7 Alcohol septal ablation in a 52-year-old woman with severe symptomatic hypertrophic cardiomyopathy. **A**, Angiography of the left coronary artery in pulmonary artery cranial angulation to clearly display the septal anatomy. The first septal perforator that was selected for ablation is shown with *white arrows*. **B**, The placement of 0.014-inch coronary wire into this septal branch. **C**, Visualization of the distal septal branch using angiographic contrast after inflation of the over-the-wire balloon. Notice that the contrast only opacifies the distal septal branch, without migration into other areas. **D**, Successful obliteration (*white arrows*) of the septal branch after injection of desiccated ethanol.

ventricle.⁷¹ At times, it may supply the basal septum incompletely and share this responsibility with the second septal perforator. Accurate assessment of the myocardial territory supplied by a septal perforator is accomplished by the angiography with selective injection of radiocontrast and concomitant use of TTE using selective injection of echo contrast (see [Figure 32.7](#)).

Continuous monitoring of the LVOTG during the procedure is essential. We place a pigtail into the left ventricle through a second arterial access. Baseline hemodynamic evaluation is performed by simultaneous LV and aortic pressure recordings at rest and with post-PVC provocation. Attention should be paid to avoid slipping of the pigtail into the LVOT and dampening of the pressure tracing from the guiding catheter. After hemodynamics, angiographic assessment of the septal anatomy is performed. After full heparinization a guiding catheter; usually a 6- or 7-Fr standard Judkins or an extra back-up catheter is used to engage the left main coronary artery through which a 0.014-inch guidewire with a soft tip is passed into the selected septal perforator branch. A short, no more than 10 mm in length and slightly larger than the vessel (usually 1.5–2 mm in diameter), an over-the-wire (OTW) angioplasty balloon is passed over the guidewire into the selected septal branch. Sometimes there is difficulty in passing the balloon into the selected septal perforator, which may be remedied by using a stiffer guidewire. Sometimes difficulty may be related to the balloon choice. In our

experience, balloons with two rather than one central marker may be more difficult to negotiate through acute angles and tortuosity in small branches. Another point to be aware of is an infrequent problem of difficulty to inject through the OTW balloon. The wire lumens of some of the new-generation low-profile OTW balloons may be compressed in angulated segments and do not allow steady infusion. The balloon is inflated to completely occlude the septal branch. It must be ensured that the balloon is placed proximally without sticking back to the main artery and fully expanded so that injected alcohol does not reflux into the main artery, mostly the LAD. If the balloon is seated very deeply into the septal branch, the injected ethanol might miss the basal septum, resulting in an unsuccessful procedure.

At this point, it is critical to verify the myocardial territory being supplied by the selected septal perforator. Both angiographic and echocardiographic confirmation must be obtained before proceeding with alcohol injection. To obtain angiographic confirmation, the operator should inject 1 to 2 cc of radiocontrast through the OTW balloon (see [Figure 32.7](#)). Contrast should be injected slowly to mimic the anticipated alcohol injection. Three things must be observed. First, the operator should ensure that the selected perforator branch indeed supplies the basal septum that is responsible for the LVOT obstruction. This can be accomplished by focusing on the site of SAM septal contact and the color Doppler–estimated site of maximal

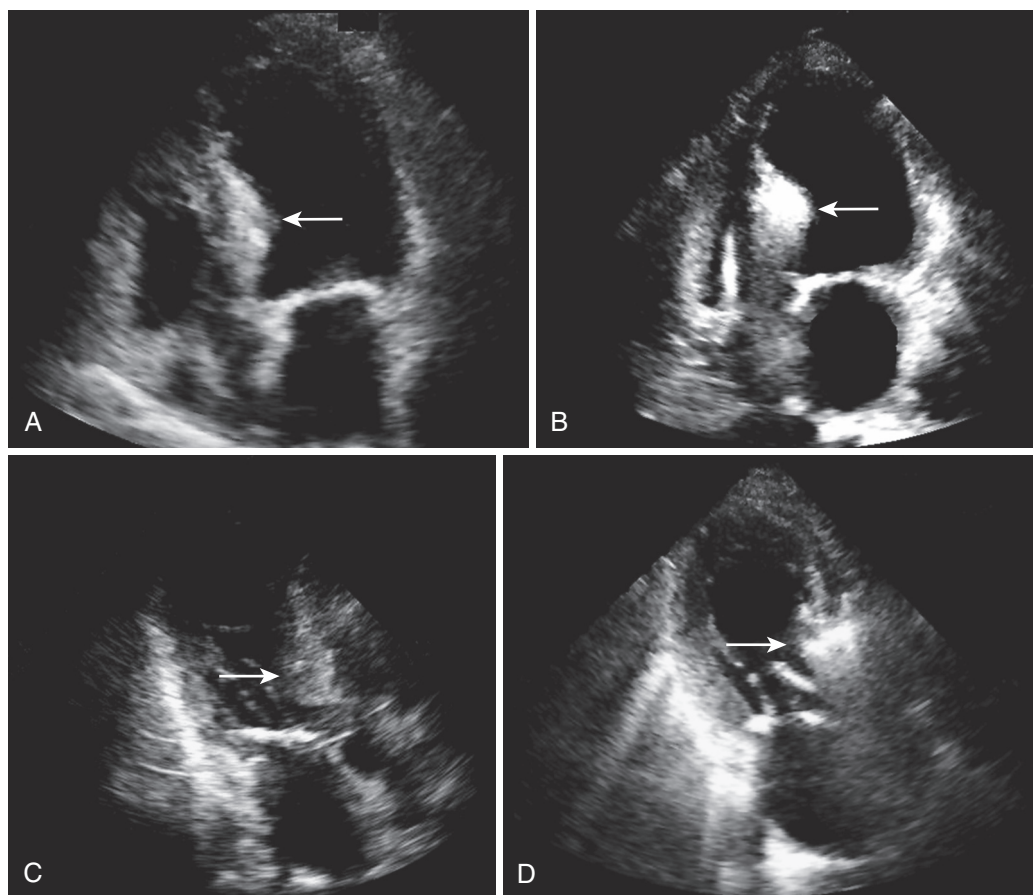


FIGURE 32.8 Echocardiographic characterization of the myocardial territory supplied by the targeted septal branch for alcohol ablation. **A** and **C**, The apical four-chamber and long-axis views before the echo contrast injection, showing the presence of severe septal hypertrophy. **B** and **D**, Respective images after injection of the echo contrast agent, delineating the myocardial territory supplied by the targeted septal branch. The white arrows point to the region of the upper septal hypertrophy.

flow acceleration. Second important point is to make sure that contrast does not reflux back into the main branch, most frequently the LAD. Third, the contrast should not reach to another coronary territory. When this happens, it is usually the right coronary artery receiving alcohol through septal collaterals. Alcohol even in a very small quantity may lead to a large MI.⁷² After angiographic confirmation, further assessment is obtained via contrast echocardiography. After carefully visualizing the septum in apical four-chamber and parasternal long-axis views, 1 to 2 cc of echo contrast is injected into the septal perforator through the OTW balloon (Figure 32.8). The operator should expect appearance of the echo contrast in the basal septum responsible for the greatest extent of septal-mitral contact. It is critical to ensure that no other myocardial territory is opacified. Appearance of contrast in the distal septum or other areas of myocardium is a contraindication to proceed ablation using that particular branch (see Figure 32.8). As a final method of confirmation, a meaningful reduction in the LVOTG during balloon inflation in the selected septal perforator is reassuring, but lack of it is not predictive of a suboptimal outcome.

Before proceeding with ethanol injection, the operator should fluoroscopically verify that the balloon has not migrated, there is no backleak of contrast, and the transvenous pacemaker continues to have a suitable pacing threshold. After the last checks and adequate analgesia,

the operator may proceed with the ethanol injection. Most experienced centers use between 1 and 2 mL of desiccated absolute ethanol. The volume may be adjusted based on the appearance of the septal anatomy and the degree of contrast washout. It has been demonstrated that a smaller amount of ethanol injection (1–2 mL) results in comparable clinical and hemodynamic improvements with reduced complication rates, especially lower rates of permanent pacemaker requirement.⁷³ The alcohol is generally injected over a 1- to 5-minute period with the balloon remaining inflated. During infusion, continuous or frequent fluoroscopy is essential to make sure that balloon has not moved. Initial echocardiographic examination after completion of alcohol infusion provides some clues about the success of the procedure. Lack of a well-demarcated target area, particularly in the presence of minimal or no gradient reduction, raises a concern of incomplete ablation. After the alcohol infusion, a reduction in the LVOTG to less than 30 mm Hg in the setting of a resting gradient greater than 50 mm Hg or a greater than 50% reduction of a provokable gradient is considered indicative of a successful procedure (Figure 32.9). This gradient reduction persists in the initial postprocedure days. Some patients do not get early gradient reduction, but most of them end up with reduced gradients 3 to 12 months later, similar to those who had early gradient decrease.⁷⁴ The inflated balloon should be left in place 5 to 10 minutes after completion of alcohol infusion.

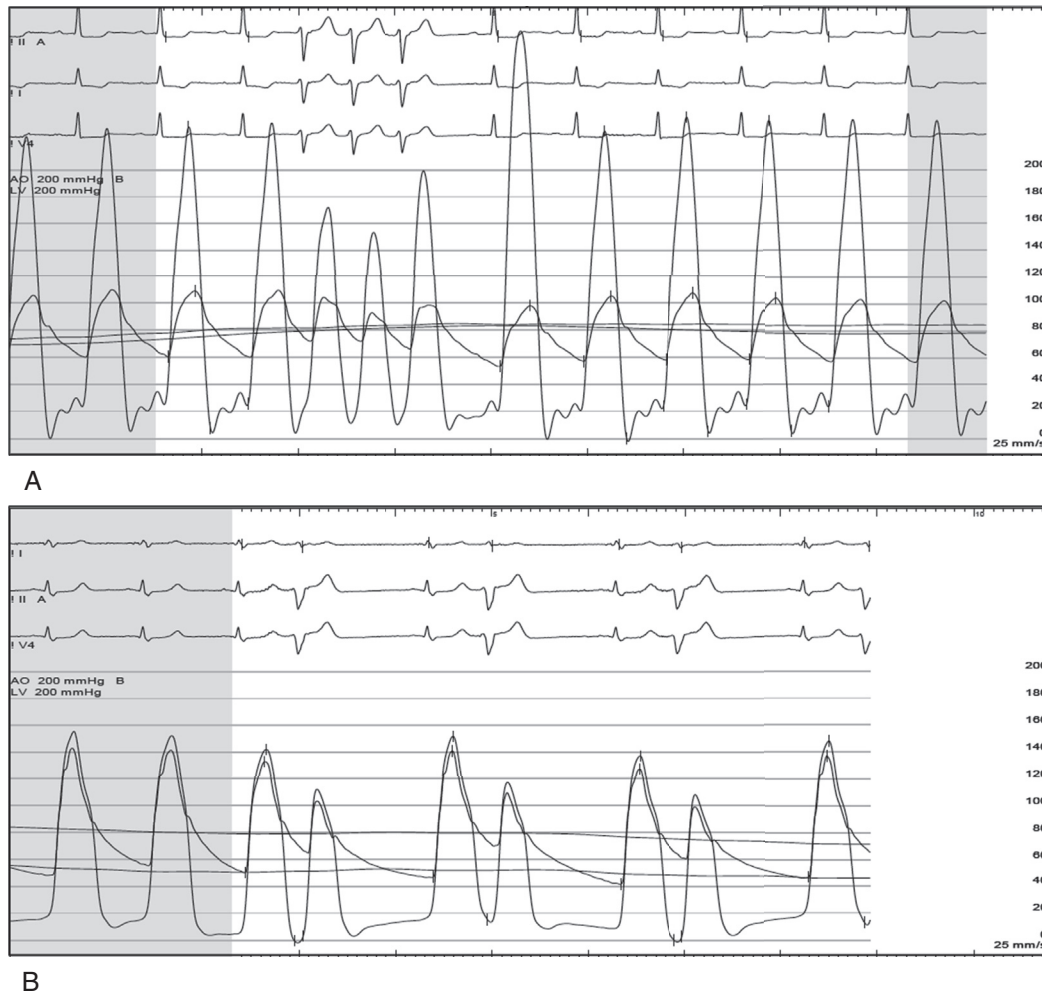


FIGURE 32.9 Hemodynamic tracings obtained from before (A) and after (B) successful alcohol septal ablation performed in a 52-year-old woman with severe symptomatic hypertrophic cardiomyopathy. The hemodynamic tracings shown in the two panels were obtained with simultaneous measurement of the left ventricular pressure waveform and aortic pressure waveform with two catheters. The *top panel* shows a significant left ventricular outflow tract (LVOT) gradient with postextrasystolic potentiation after premature ventricular contractions (Brockenbrough-Braunwald-Morrow sign). After a successful alcohol septal ablation procedure, there was a complete elimination of the LVOT gradient as well as the Brockenbrough-Braunwald-Morrow sign (B).

Before disengaging the balloon from the septal vessel, the guidewire is replaced into the septal branch to facilitate a smooth and quick removal of the balloon from the coronary circulation. As a final step, angiography of the left coronary artery is performed to document the occlusion of the septal branch and to verify the integrity of the rest of the coronary circulation.

Postprocedurally, all patients should be monitored in an intensive care unit setting for at least 48 hours with close rhythm and hemodynamic monitoring as well as serial cardiac enzyme measurements. The transvenous pacing wire may be discontinued after 24 to 48 hours if there are no bradyarrhythmias or heart block that necessitates a longer observation or permanent pacemaker implantation. The amount of creatine kinase-MB (CK-MB) elevation after ablation ranges between 800 to 1200 IU/L, although this is variable depending on the amount of alcohol injected, vessel size, and method of enzyme measurement. In most centers, the patient is transferred to a regular nursing floor for an additional 2 to 3 days to observe for postprocedural complications before discharge.

RESULTS. Alcohol septal ablation is a safe procedure. Contemporary studies report a hospital mortality rate of 1% or less with ASA.^{69,75,76} ASA reduces LVOTG in more than 90% of patients by 70% to 80%.^{69,77,78} Gradient reduction demonstrates a triphasic response, and it may take up to 3 months to completely manifest its effect on LVOTG.⁷⁴ An acute reduction in LVOTG immediately after successful ASA is generally followed by an increase in the gradient to the baseline level within 3 days followed by a decrease back to the immediate postablation level within 3 months. Some patients do not get early gradient reduction. But most of them ultimately reach to lower gradients similar to those who had an early gradient decrease.⁶⁶ The acute decrease in the LVOTG reflects a loss of septal contractility caused by ischemia, necrosis, and stunning of the septal myocardium. The early recovery of gradient after ASA is thought to reflect the recovery of the septal myocardium from stunning along with myocardial edema that accompanies necrosis. Over the course of the next 3 months, there is thinning of the infarcted septum and LVOT remodeling, leading to sustained and more permanent reduction in gradients and resulting in improvement in MR and reduction

in pressure and size of the left atrium, which may promote a decreased incidence of AF and amelioration of pulmonary hypertension.^{79,80} Reduction of the pressure overload in the LV leads to regression of hypertrophy and improvement in diastolic function.⁸¹⁻⁸³ A reduction in LVOTG results in improvement of symptoms.^{80,84-87}

Studies have consistently demonstrated improvement in symptoms and exercise capacity.^{80,88} In an earlier study with a follow-up of up to 8 years, a further gradient reduction beyond 1 year was observed.⁸⁹ Midterm results from larger studies confirmed the sustained benefit from ASA. In one of these studies in which investigators studied 953 patients who underwent ASA between 2000 and 2017, the mean follow-up period was 6 years. Kaplan-Meier analysis revealed 5-, 10-, and 15-year survival rates of 95.8%, 88.3%, and 79.7%, respectively.⁹⁰ In a two-center study from Europe including 470 consecutive patients with HCM who underwent ASA, the 10-year survival rate was 88%, which was similar to that in the background population. The incidences of ventricular tachycardia episodes and SCD were low.⁹¹ This and other studies suggest ASA reduces the risk of SCD.^{69,92}

COMPLICATIONS. Conduction disturbances is common after ASA. In contrast to the left bundle branch block commonly seen after SM, a right bundle branch block is observed in about 50% of cases after ASA.^{93,94} Early reports showed a high incidence, up to 20%, of complete heart block requiring permanent pacemaker implantation. With accumulating experience and iterative changes, including careful identification of the target site by contrast echocardiography, slowing the injection speed, and minimizing the alcohol volume, the rate of pacemaker requirement in contemporary practice is around 10%.⁶⁹ The rate of life-threatening complications such as leakage of alcohol to unintended vessels and territories, coronary dissections, malfunction of the pacemaker in the setting of complete heart block, and right ventricular perforation with pacemaker leading to cardiac tamponade are rare in experienced high-volume centers where meticulous attention is paid to technical details. Ventricular arrhythmias can be seen during the procedure in the early postprocedure period but are not predictive of a poor clinical outcome. Unlike SM, ASA results in a large myocardial scar that has been speculated to serve as a nidus for malignant ventricular tachyarrhythmias. A retrospective study reporting fourfold increase in ICD discharges in ASA patients compared with those who underwent SM raised a serious concern.⁹⁵ However, subsequent studies showing very low sudden death and ICD discharge rates following ASA have not confirmed this initial observation.^{78,90,92,96,97}

Comparison of Alcohol Septal Ablation and Septal Myectomy

Current ACC/AHA as well as European Society of Cardiology (ESC) guidelines consider SM and ASA not as two unrelated therapeutic modalities but as two distinct techniques targeting one aim, to reduce LVOTO via septal reduction.^{7,45} There have been no randomized controlled trials comparing SM and ASA, and it is highly unlikely there will be any in the future. Multiple observational studies and a number of meta-analyses comparing the safety and

efficacy of ASA and SM demonstrated similar safety and hemodynamic and functional improvement. These findings support the US and the European guidelines approaching SRT as the treatment strategy with two different procedures available for relief of LVOTO.^{78,96,98}

Another area that the current guidelines emphasize is the specialized high-volume HCM centers staffed by HCM experts from diverse fields, including clinical, imaging, electrophysiology, and heart failure cardiology and cardiac surgeons and interventional cardiologists with experience in SM and ASA, respectively. Best practice would require HCM team equipped with all the available therapeutic modalities approach the patient by asking what the most appropriate treatment for the specific patient would be. Accumulated evidence over the decades provide basis for recommending either SM or ASA for most patients with HCM. A minority of patients are candidates either for SM but not for ASA or vice versa. The 2014 ESC and 2020 ACC/AHA guidelines state that patients who require concomitant valvular or coronary bypass or some other type of cardiac surgery should be treated with SM.^{7,45} In patients for whom SM is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, ASA is recommended. In the 2011 ACC/AHA guidelines, ASA for younger patients was given a Class III recommendation. But data that accumulated over the past decade demonstrated ASA is safe and effective in younger patients as it is in older patients.⁹⁹⁻¹⁰¹ The largest of these studies reported the 30-day and long-term (mean follow-up, 5.4 ± 42 years) outcome of 1197 patients who were treated with ASA in seven tertiary centers in four European countries.¹⁰¹ Investigators divided patients into three groups: 405 older (65 years of age and older), 423 middle-aged,⁵¹⁻⁶⁴ and 369 young (50 years of age and younger) patients.¹⁰¹ The 30-day mortality and pacemaker implantation rates were lower in young compared with older patients (0.3% vs 2% [$P = .03$] and 8% vs 16% [$P < .001$], respectively). Ninety-five percent of young patients were in NYHA functional Class I or II at last follow-up. Annual mortality rates of young, middle-aged, and older patients were 1%, 2%, and 5%, respectively ($P < .01$). Higher residual gradients and alcohol volume of 2.5 mL or greater were associated by higher long-term mortality. Of the young cohort, 82 patients were 35 years old or younger. Their outcomes were also equally good. The author of the editorial for this article summarized the main message of the study “although the present study, a comparison of outcomes of ASA among different age groups, does not provide a direct comparison of outcomes after ASA and myectomy in younger patients, it provides reassuring data regarding the efficacy and safety of ASA in such patients.”¹⁰² In the current ACC/AHA and ESC guidelines, there are no age-based recommendations for adult patients with HCM.

Alcohol septal ablation may be less effective with extreme septal thickness. Current ACC/AHA guidelines state that the effectiveness of ASA is limited in patients with an extremely thick septum. In the two studies reported to date, the degree of gradient reduction with ASA was correlated with the septal thickness.^{103,104} In another study, the extent of basal segments hypertrophy, rather than

only the antero-septal hypertrophy, predicted success of ablation.¹⁰⁵ These data suggest that severity of the septal thickness should be taken into account in choosing the SRT modality, but there is lack of strong data supporting a categorical cutoff point of 30 mm.

Postprocedural gradients are generally slightly higher after ASA compared with after SM. However, this difference has no impact for long-term survival or well-being.¹⁰⁶ Another difference between the two techniques is the need for repeat SRT procedures. In a systematic analysis and meta-analysis including 4804 patients, the rates of repeat procedures were 7.7% after ASA and 1.7% after SM. In the same study, pacemaker rates were 10% after ASA and 4.4% after SM.⁷⁸ On the other hand, surgical complications such as major bleeding, surgical infections, and repeat sternotomy are not seen with ASA.

NOVEL TECHNIQUES FOR SEPTAL REDUCTION USING NONALCOHOL SUBSTANCES

There has been some experience with nonalcohol substances for SRT. The series available for this are small and definitive conclusions are hard to reach for the general population. A small nonrandomized pilot study of 20 patients suggested that SRT using coil embolization is feasible and may be more efficacious in preventing complete heart block.¹⁰⁷ At 6-month follow-up, there were significant improvements in NYHA functional class and peak oxygen consumption. Follow-up echocardiography demonstrated a significant reduction in septal thickness and LVOTG.¹⁰⁷ Similar results have been reported for ethylene vinyl alcohol copolymer.¹⁰⁸ A small study of 25 patients reported no deaths at 1-year follow-up along with significant reductions in mean septal thickness and LVOTG. Two patients had complete heart block, and three patients had no reduction in LVOTG over follow-up.¹⁰⁸ Radiofrequency ablation is also used for septal ablation.¹⁰⁹

SHARED DECISION MAKING

An important area emphasized in the ACC/AHA and ESC guidelines is involving the patient in the decision making. Shared decision making is now the cornerstone of the management process of complex diseases in cardiovascular medicine. This entails a dialogue between the patient and the providers to work together to select the best course of action after fully considering the pros and cons of the available treatment options as well as the values, expectations, and preferences of the patients. It is imperative that patients should be fully informed about all aspects of SM and ASA in an unbiased way so they take into account the potential limitations of both techniques. Without fully understanding the specific implications in a given case, ASA appears the more attractive option to most, if not, all patients. Although the issues associated with surgery such as the need for general anesthesia, pain and discomfort, long recovery time, and surgical scar would be easy for patients to appreciate, physicians should also explain the limitations of ASA such as higher permanent

pacemaker requirement, slightly lower success rate, more frequent need for a second procedure, and lack of follow-up data dating for as many years as SM data do.

HYPERTROPHIC CARDIOMYOPATHY CENTERS

Current ESC and ACC/AHA guidelines emphasize the importance of specialized high-volume HCM centers. Most of the data supporting the guideline's statements about SM originate from such centers. Accordingly, as a caveat, the applicability of the published data to the institution where the procedure will be performed should be taken into account in the decision making. Although published studies generally report a very low early mortality rate, some approaching to 0%, these publications originate from a very limited number of North American and even from smaller number of European centers. On the other hand, real-world practice appears to be rather different. In a 2016 study, investigators used the data from the US Nationwide Inpatient Sample 2003 to 2011 database to analyze the impact of case numbers on mortality and other outcomes after SM and ASA by comparing US institutions grouped in three tertiles by volume.⁷⁶ During the study period, most US centers performed fewer than 10 SM and ASA procedures annually. Of the 11,248 patients who were treated with SRT, 57% underwent SM, and 43% had ASA. The incidence of in-hospital death was lower in the high-volume centers compared with low-volume centers after SM (15.6%, 9.6%, and 3.8%, respectively; $P < .001$) and after ASA (2.3%, 0.8%, and 0.6%, respectively; $P = .02$). Low SM volume was associated with worse outcomes, including higher mortality rate, longer length of stay, and higher costs. On the other hand, low ASA volume was not associated with worse outcomes after adjustment for baseline characteristics. These data highlight the value of high-volume centers and HCM teams focusing on individualizing the treatment decision according to the unique characteristics of every patient. In regions where large SM experience is lacking, the availability of ASA expertise can serve not all but most of the patients that need treatment for LVOTO. These data should also motivate the cardiac surgery community to work toward wider availability of surgical expertise.

REFERENCES

1. Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J*. 1958;20(1):1-8.
2. Maron MS, Olivetto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation*. 2006;114(21):2232-2239.
3. Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2015;65(12):1249-1254.
4. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA*. 2002;287(10):1308-1320.
5. Maron MS, Hellawell JL, Lucove JC, Farzaneh-Far R, Olivetto I. Occurrence of clinically diagnosed hypertrophic cardiomyopathy in the United States. *Am J Cardiol*. 2016;117(10):1651-1654.
6. Maron BJ, Peterson EE, Maron MS, Peterson JE. Prevalence of hypertrophic cardiomyopathy in an outpatient population referred for echocardiographic study. *Am J Cardiol*. 1994;73(8):577-580.
7. Writing Committee Members, Ommen SR, Mital S, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Thorac Cardiovasc Surg*. 2021;162(1):e23-e106.

8. Maron BJ. Distinguishing hypertrophic cardiomyopathy from athlete's heart physiological remodelling: clinical significance, diagnostic strategies and implications for preparticipation screening. *Br J Sports Med.* 2009; 43(9):649-656.
9. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. *N Engl J Med.* 2018;379(7):655-668.
10. Maron MS, Olivetto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med.* 2003;348(4):295-303.
11. Braunwald E, Brockenbrough EC, Morrow AG. Hypertrophic subaortic stenosis—a broadened concept. *Circulation.* 1962;26:161-165.
12. Ayoub C, Geske JB, Larsen CM, Scott CG, Klarich KW, Pellikka PA. Comparison of Valsalva maneuver, amyl nitrite, and exercise echocardiography to demonstrate latent left ventricular outflow obstruction in hypertrophic cardiomyopathy. *Am J Cardiol.* 2017;120(12):2265-2271.
13. Geske JB, Sorajja P, Ommen SR, Nishimura RA. Left ventricular outflow tract gradient variability in hypertrophic cardiomyopathy. *Clin Cardiol.* 2009; 32(7):397-402.
14. Maron BJ, Nishimura RA, Danielson GK. Pitfalls in clinical recognition and a novel operative approach for hypertrophic cardiomyopathy with severe outflow obstruction due to anomalous papillary muscle. *Circulation.* 1998; 98(23):2505-2508.
15. Elesber A, Nishimura RA, Rihal CS, Ommen SR, Schaff HV, Holmes Jr DR. Utility of isoproterenol to provoke outflow tract gradients in patients with hypertrophic cardiomyopathy. *Am J Cardiol.* 2008;101(4):516-520.
16. Maron BJ, Epstein SE, Roberts WC. Hypertrophic cardiomyopathy and transmural myocardial infarction without significant atherosclerosis of the extramural coronary arteries. *Am J Cardiol.* 1979;43(6):1086-1102.
17. Basso C, Thiene G, Corrado D, Buja G, Melacini P, Nava A. Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia. *Hum Pathol.* 2000;31(8):988-998.
18. Choudhury L, Mahrholdt H, Wagner A, et al. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2002;40(12):2156-2164.
19. Dilsizian V, Bonow RO, Epstein SE, Fananapazir L. Myocardial ischemia detected by thallium scintigraphy is frequently related to cardiac arrest and syncope in young patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 1993;22(3):796-804.
20. Schwartzkopff B, Mundhenke M, Strauer BE. Alterations of the architecture of subendocardial arterioles in patients with hypertrophic cardiomyopathy and impaired coronary vasodilator reserve: a possible cause for myocardial ischemia. *J Am Coll Cardiol.* 1998;31(5):1089-1096.
21. Raphael CE, Cooper R, Parker KH, et al. Mechanisms of myocardial ischemia in hypertrophic cardiomyopathy: insights from wave intensity analysis and magnetic resonance. *J Am Coll Cardiol.* 2016;68(15):1651-1660.
22. Frenneaux MP, Counihan PJ, Caforio AL, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. *Circulation.* 1990;82(6):1995-2002.
23. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. *Circulation.* 1997; 96(9):2987-2991.
24. Olivetto I, Maron BJ, Montereggi A, Mazzuoli F, Dolara A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 1999;33(7):2044-2051.
25. Wigle ED, Adelman AG, Auger P, Marquis Y. Mitral regurgitation in muscular subaortic stenosis. *Am J Cardiol.* 1969;24(5):698-706.
26. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy. Clinical spectrum and treatment. *Circulation.* 1995;92(7):1680-1692.
27. Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy. The importance of the site and the extent of hypertrophy. A review. *Prog Cardiovasc Dis.* 1985;28(1):1-83.
28. Hang D, Schaff HV, Nishimura RA, et al. Accuracy of jet direction on doppler echocardiography in identifying the etiology of mitral regurgitation in obstructive hypertrophic cardiomyopathy. *J Am Soc Echocardiogr.* 2019; 32(3):333-340.
29. Klues HG, Schiffrers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol.* 1995;26(7):1699-1708.
30. Nampiaparampil RG, Swistel DG, Schlame M, Saric M, Sherrid MV. Intraoperative two- and three-dimensional transesophageal echocardiography in combined myectomy-mitral operations for hypertrophic cardiomyopathy. *J Am Soc Echocardiogr.* 2018;31(3):275-288.
31. Faber L, Seggewiss H, Welge D, et al. Echo-guided percutaneous septal ablation for symptomatic hypertrophic obstructive cardiomyopathy: 7 years of experience. *Eur J Echocardiogr.* 2004;5(5):347-355.
32. Nagueh SF, Bierig SM, Budoff MJ, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with hypertrophic cardiomyopathy: endorsed by the American Society of Nuclear Cardiology, Society for Cardiovascular Magnetic Resonance, and Society of Cardiovascular Computed Tomography. *J Am Soc Echocardiogr.* 2011;24(5):473-498.
33. Rowin EJ, Maron BJ, Olivetto I, Maron MS. Role of exercise testing in hypertrophic cardiomyopathy. *JACC Cardiovasc Imaging.* 2017;10(11):1374-1386.
34. Coats CJ, Rantell K, Bartnik A, et al. Cardiopulmonary exercise testing and prognosis in hypertrophic cardiomyopathy. *Circ Heart Fail.* 2015;8(6):1022-1031.
35. Habib M, Adler A, Fardini K, et al. Progression of myocardial fibrosis in hypertrophic cardiomyopathy: a cardiac magnetic resonance study. *JACC Cardiovasc Imaging.* 2021;14(5):947-958.
36. Brugada P, Bar FW, de Zwaan C, Roy D, Green M, Wellens HJ. "Sawfish" systolic narrowing of the left anterior descending coronary artery: an angiographic sign of hypertrophic cardiomyopathy. *Circulation.* 1982;66(4):800-803.
37. Basso C, Thiene G, Mackey-Bojack S, Frigo AC, Corrado D, Maron BJ. Myocardial bridging, a frequent component of the hypertrophic cardiomyopathy phenotype, lacks systematic association with sudden cardiac death. *Eur Heart J.* 2009;30(13):1627-1634.
38. Yetman AT, McCrindle BW, MacDonald C, Freedom RM, Gow R. Myocardial bridging in children with hypertrophic cardiomyopathy—a risk factor for sudden death. *N Engl J Med.* 1998;339(17):1201-1209.
39. Sorajja P, Ommen SR, Nishimura RA, Gersh BJ, Tajik AJ, Holmes DR. Myocardial bridging in adult patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2003;42(5):889-894.
40. Mohiddin SA, Begley D, Shih J, Fananapazir L. Myocardial bridging does not predict sudden death in children with hypertrophic cardiomyopathy but is associated with more severe cardiac disease. *J Am Coll Cardiol.* 2000; 36(7):2270-2278.
41. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. *N Engl J Med.* 1997;336(11):775-785.
42. Sorajja P, Ommen SR, Nishimura RA, Gersh BJ, Berger PB, Tajik AJ. Adverse prognosis of patients with hypertrophic cardiomyopathy who have epicardial coronary artery disease. *Circulation.* 2003;108(19):2342-2348.
43. Maron BJ, Chaitman BR, Ackerman MJ, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. *Circulation.* 2004;109(22):2807-2816.
44. Semsarian C, Ahmad I, Giewat M, et al. The L-type calcium channel inhibitor diltiazem prevents cardiomyopathy in a mouse model. *J Clin Invest.* 2002;109(8):1013-1020.
45. Authors/Task Force Members, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J.* 2014;35(39):2733-2779.
46. Bourmayan C, Razavi A, Fournier C, et al. Effect of propranolol on left ventricular relaxation in hypertrophic cardiomyopathy: an echographic study. *Am Heart J.* 1985;109(6):1311-1316.
47. Alvares RF, Goodwin JF. Non-invasive assessment of diastolic function in hypertrophic cardiomyopathy on and off beta adrenergic blocking drugs. *Br Heart J.* 1982;48(3):204-212.
48. Dybro AM, Rasmussen TB, Nielsen RR, Andersen MJ, Jensen MK, Poulsen SH. Randomized trial of metoprolol in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2021;78(25):2505-2517.
49. Sherrid MV, Barac I, McKenna WJ, et al. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2005;45(8):1251-1258.
50. Olivetto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2020;396(10253):759-769.
51. Hegde SM, Lester SJ, Solomon SD, et al. Effect of mavacamten on echocardiographic features in symptomatic patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2021;78(25):2518-2532.
52. Smedira NG, Lytle BW, Lever HM, et al. Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy. *Ann Thorac Surg.* 2008;85(1):127-133.
53. Ommen SR, Maron BJ, Olivetto I, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2005;46(3):470-476.
54. Veselka J, Faber L, Liebrechts M, et al. Outcome of alcohol septal ablation in mildly symptomatic patients with hypertrophic obstructive cardiomyopathy: a long-term follow-up study based on the Euro-Alcohol Septal Ablation Registry. *J Am Heart Assoc.* 2017;6(5):e005735.
55. Jones BM, Krishnaswamy A, Smedira NG, Desai MY, Tuzcu EM, Kapadia SR. How symptomatic should a hypertrophic obstructive cardiomyopathy patient be to consider alcohol septal ablation? *J Am Heart Assoc.* 2017;6(5):e006292.
56. Sorajja P, Nishimura RA, Gersh BJ, et al. Outcome of mildly symptomatic or asymptomatic obstructive hypertrophic cardiomyopathy: a long-term follow-up study. *J Am Coll Cardiol.* 2009;54(3):234-241.
57. Goodwin JF, Hollman A, Cleland WP, Teare D. Obstructive cardiomyopathy simulating aortic stenosis. *Br Heart J.* 1960;22:403-414.
58. Morrow AG. Hypertrophic subaortic stenosis. Operative methods utilized to relieve left ventricular outflow obstruction. *J Thorac Cardiovasc Surg.* 1978;76(4):423-430.
59. Maron BJ, Dearani JA, Ommen SR, et al. The case for surgery in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2004;44(10):2044-2053.
60. Wei LM, Thibault DP, Rankin JS, et al. Contemporary surgical management of hypertrophic cardiomyopathy in the United States. *Ann Thorac Surg.* 2019;107(2):460-466.
61. Alashi A, Desai RM, Khullar T, et al. Different histopathologic diagnoses in patients with clinically diagnosed hypertrophic cardiomyopathy after surgical myectomy. *Circulation.* 2019;140(4):344-346.
62. Cui H, Schaff HV, Lentz Carvalho J, et al. Myocardial histopathology in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2021;77(17):2159-2170.

63. Nguyen A, Schaff HV, Hang D, et al. Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic cardiomyopathy: a propensity score-matched cohort. *J Thorac Cardiovasc Surg.* 2019;157(1):306-315.e3.
64. Mitra A, Ghosh RK, Bandyopadhyay D, Ghosh GC, Kalra A, Lavie CJ. Significance of pulmonary hypertension in hypertrophic cardiomyopathy. *Curr Probl Cardiol.* 2020;45(6):100398.
65. Kobayashi T, Dhillon A, Popovic Z, et al. Differences in global and regional left ventricular myocardial mechanics in various morphologic subtypes of patients with obstructive hypertrophic cardiomyopathy referred for ventricular septal myotomy/myectomy. *Am J Cardiol.* 2014;113(11):1879-1885.
66. Geske JB, Driver CN, Yogeswaran V, Ommen SR, Schaff HV. Comparison of expected and observed outcomes for septal myectomy in hypertrophic obstructive cardiomyopathy. *Am Heart J.* 2020;221:159-164.
67. Maron BJ, Dearani JA, Maron MS, et al. Why we need more septal myectomy surgeons: an emerging recognition. *J Thorac Cardiovasc Surg.* 2017;154(5):1681-1685.
68. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. *Lancet.* 1995;346(8969):211-214.
69. Veselka J, Jensen MK, Liebrechts M, et al. Long-term clinical outcome after alcohol septal ablation for obstructive hypertrophic cardiomyopathy: results from the Euro-ASA registry. *Eur Heart J.* 2016;37(19):1517-1523.
70. Holmes Jr DR, Valeti US, Nishimura RA. Alcohol septal ablation for hypertrophic cardiomyopathy: indications and technique. *Catheter Cardiovasc Interv.* 2005;66(3):375-389.
71. Singh M, Edwards WD, Holmes Jr DR, Tajil AJ, Nishimura RA. Anatomy of the first septal perforating artery: a study with implications for ablation therapy for hypertrophic cardiomyopathy. *Mayo Clin Proc.* 2001;76(8):799-802.
72. Agarwal SC, Purcell IF, Furniss SS. Apical myocardial injury caused by collateralisation of a septal artery during ethanol septal ablation. *Heart.* 2005;91(1):e2.
73. Veselka J, Duchonova R, Prochazkova S, Palenickova J, Sorajja P, Tesar D. Effects of varying ethanol dosing in percutaneous septal ablation for obstructive hypertrophic cardiomyopathy on early hemodynamic changes. *Am J Cardiol.* 2005;95(5):675-678.
74. Yoerger DM, Picard MH, Palacios IF, Vlahakes GJ, Lowry PA, Fifer MA. Time course of pressure gradient response after first alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Am J Cardiol.* 2006;97(10):1511-1514.
75. Seggewiss H. Current status of alcohol septal ablation for patients with hypertrophic cardiomyopathy. *Curr Cardiol Rep.* 2001;3(2):160-166.
76. Kim LK, Swaminathan RV, Looser P, et al. Hospital volume outcomes after septal myectomy and alcohol septal ablation for treatment of obstructive hypertrophic cardiomyopathy: US Nationwide Inpatient Database, 2003-2011. *JAMA Cardiol.* 2016;1(3):324-332.
77. Rigopoulos AG, Seggewiss H. A decade of percutaneous septal ablation in hypertrophic cardiomyopathy. *Circ J.* 2011;75(1):28-37.
78. Liebrechts M, Vriesendorp PA, Mahmoodi BK, Schinkel AF, Michels M, ten Berg JM. A systematic review and meta-analysis of long-term outcomes after septal reduction therapy in patients with hypertrophic cardiomyopathy. *JACC Heart Fail.* 2015;3(11):896-905.
79. Sorajja P, Nishimura RA, Ommen SR, Rihal CS, Gersh BJ, Holmes Jr DR. Effect of septal ablation on myocardial relaxation and left atrial pressure in hypertrophic cardiomyopathy: an invasive hemodynamic study. *JACC Cardiovasc Interv.* 2008;1(5):552-560.
80. Faber L, Seggewiss H, Gleichmann U. Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: results with respect to intraprocedural myocardial contrast echocardiography. *Circulation.* 1998;98(22):2415-2421.
81. Rubinshtein R, Glockner JF, Ommen SR, et al. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. *Circ Heart Fail.* 2010;3(1):51-58.
82. O'Hanlon R, Grasso A, Roughton M, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2010;56(11):867-874.
83. Bruder O, Wagner A, Jensen CJ, et al. Myocardial scar visualized by cardiovascular magnetic resonance imaging predicts major adverse events in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2010;56(11):875-887.
84. van Dockum WG, Beek AM, ten Cate FJ, et al. Early onset and progression of left ventricular remodeling after alcohol septal ablation in hypertrophic obstructive cardiomyopathy. *Circulation.* 2005;111(19):2503-2508.
85. Nagueh SF, Lakkis NM, Middleton KJ, et al. Changes in left ventricular filling and left atrial function six months after nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol.* 1999;34(4):1123-1128.
86. Matsuda J, Kitamura M, Takayama M, et al. Chronic phase improvements in electrocardiographic and echocardiographic manifestations of left ventricular hypertrophy after alcohol septal ablation for drug-refractory hypertrophic obstructive cardiomyopathy. *Heart Vessels.* 2018;33(3):246-254.
87. Chen YZ, Qiao SB, Hu FH, et al. Biventricular reverse remodeling after successful alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Am J Cardiol.* 2015;115(4):493-498.
88. Ruzyllo W, Chojnowska L, Demkow M, et al. Left ventricular outflow tract gradient decrease with non-surgical myocardial reduction improves exercise capacity in patients with hypertrophic obstructive cardiomyopathy. *Eur Heart J.* 2000;21(9):770-777.
89. Seggewiss H, Rigopoulos A, Welge D, Ziemssen P, Faber L. Long-term follow-up after percutaneous septal ablation in hypertrophic obstructive cardiomyopathy. *Clin Res Cardiol.* 2007;96(12):856-863.
90. Batzner A, Pfeiffer B, Neugebauer A, Aicha D, Blank C, Seggewiss H. Survival after alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol.* 2018;72(24):3087-3094.
91. Jensen MK, Prinz C, Horstkotte D, et al. Alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy: low incidence of sudden cardiac death and reduced risk profile. *Heart.* 2013;99(14):1012-1017.
92. Sorajja P, Ommen SR, Holmes Jr DR, et al. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Circulation.* 2012;126(20):2374-2380.
93. Chen AA, Palacios IF, Mela T, et al. Acute predictors of subacute complete heart block after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Am J Cardiol.* 2006;97(2):264-269.
94. Faber L, Welge D, Fassbender D, Schmidt HK, Horstkotte D, Seggewiss H. Percutaneous septal ablation for symptomatic hypertrophic obstructive cardiomyopathy: managing the risk of procedure-related AV conduction disturbances. *Int J Cardiol.* 2007;119(2):163-167.
95. Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA.* 2007;298(4):405-412.
96. Agarwal S, Tuzcu EM, Desai MY, et al. Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2010;55(8):823-834.
97. Balt JC, Wijffels MC, Boersma LV, Wever EF, ten Berg JM. Continuous rhythm monitoring for ventricular arrhythmias after alcohol septal ablation for hypertrophic cardiomyopathy. *Heart.* 2014;100(23):1865-1870.
98. Leonardi RA, Kransdorf EP, Simel DL, Wang A. Meta-analyses of septal reduction therapies for obstructive hypertrophic cardiomyopathy: comparative rates of overall mortality and sudden cardiac death after treatment. *Circ Cardiovasc Interv.* 2010;3(2):97-104.
99. Veselka J, Krejci J, Tomasov P, et al. Survival of patients ≤ 50 years of age after alcohol septal ablation for hypertrophic obstructive cardiomyopathy. *Can J Cardiol.* 2014;30(6):634-638.
100. Liebrechts M, Steggerda RC, Vriesendorp PA, et al. Long-term outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy in the young and the elderly. *JACC Cardiovasc Interv.* 2016;9(5):463-469.
101. Liebrechts M, Faber L, Jensen MK, et al. Outcomes of alcohol septal ablation in younger patients with obstructive hypertrophic cardiomyopathy. *JACC Cardiovasc Interv.* 2017;10(11):1134-1143.
102. Fifer MA. Septal ablation in younger patients: is it time to update the guidelines? *JACC Cardiovasc Interv.* 2017;10(11):1144-1146.
103. Yang YJ, Fan CM, Yuan JQ, et al. Effectiveness of alcohol septal ablation in obstructive hypertrophic cardiomyopathy with versus without extreme septal hypertrophy. *J Invasive Cardiol.* 2016;28(3):99-103.
104. Lu M, Du H, Gao Z, et al. Predictors of outcome after alcohol septal ablation for hypertrophic obstructive cardiomyopathy: an echocardiography and cardiovascular magnetic resonance imaging study. *Circ Cardiovasc Interv.* 2016;9(3):e002675.
105. Kitamura M, Amano Y, Takayama M, et al. Usefulness of non-anteroseptal region left ventricular hypertrophy using cardiac magnetic resonance to predict repeat alcohol septal ablation for refractory obstructive hypertrophic cardiomyopathy. *Am J Cardiol.* 2017;120(1):124-130.
106. Steggerda RC, Damman K, Balt JC, Liebrechts M, ten Berg JM, van den Berg MP. Periprocedural complications and long-term outcome after alcohol septal ablation versus surgical myectomy in hypertrophic obstructive cardiomyopathy: a single-center experience. *JACC Cardiovasc Interv.* 2014;7(11):1227-1234.
107. Durand E, Mousseaux E, Coste P, et al. Non-surgical septal myocardial reduction by coil embolization for hypertrophic obstructive cardiomyopathy: early and 6 months follow-up. *Eur Heart J.* 2008;29(3):348-355.
108. Asil S, Kaya B, Canpolat U, et al. Septal reduction therapy using nonalcohol agent in hypertrophic obstructive cardiomyopathy: single center experience. *Catheter Cardiovasc Interv.* 2018;92(3):557-565.
109. Shelke AB, Menon R, Kapadiya A, et al. A novel approach in the use of radiofrequency catheter ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy. *Indian Heart J.* 2016;68(5):618-623.



33

Patent Foramen Ovale, Atrial Septal Defect, Left Atrial Appendage, And Ventricular Septal Defect Closure

SACHIN S. GOEL, JOE AOUN, LOURDES R. PRIETO, AND SAMIR R. KAPADIA

PATENT FORAMEN OVALE, 596

Introduction, 596

Developmental Anatomy of the Atrial Septum, 596

Clinical Presentation, 597

Diagnosis, 598

Management, 599

Medical Therapy, 600

Transcatheter Patent Foramen Ovale Closure, 600

Randomized Trials of Patent Foramen Ovale Closure for Cryptogenic Stroke, 600

Indications for Transcatheter Patent Foramen Ovale Closure, 601

Devices, 602

Procedural Details, 602

Postprocedure Care, 604

Complications, 604

ATRIAL SEPTAL DEFECT CLOSURE, 604

Introduction, 604

Anatomy, 605

Pathophysiology, 605

Clinical Presentation, 605

Diagnosis, 605

Cardiac Catheterization, 606

Management and Indications for Atrial Septal Defect Closure, 606

Devices for Atrial Septal Defect Closure, 607

Procedural Details, 607

Postprocedure Care, 609

Large Atrial Septal Defect with Deficient Rims, 609

Multiple or Fenestrated Defects, 610

Iatrogenic Atrial Septal Defects After

Transcatheter Mitral Interventions, 610

Complications, 610

Clinical Trial Data, 611

LEFT ATRIAL APPENDAGE CLOSURE, 611

Introduction, 611

Medical Therapy for Stroke Prevention in Atrial Fibrillation, 611

Left Atrial Appendage Anatomy, 611

Surgical Left Atrial Appendage Exclusion, 612

Transcatheter Left Atrial Appendage Closure, 612

Imaging for Left Atrial Appendage Closure, 612

Watchman and Watchman FLX Devices, 612

Procedure, 612

Data for the Watchman Device, 612

Peridevice Leak, 614

Device-Related Thrombus, 614

Amplatzer Cardiac Plug, 615

Data for Amplatzer Cardiac Plug Device, 615

Amulet versus Watchman, 615

LARIAT Device, 616

Other Left Atrial Appendage Closure Devices, 616

VENTRICULAR SEPTAL DEFECT, 616

Introduction, 616

Anatomy, 617

Pathophysiology, 617

Clinical Presentation, 617

Diagnosis, 617

Management and Indications for Ventricular Septal Defect Closure, 618

Devices for Transcatheter Ventricular Septal Defect Closure, 618

Contraindications for Closure (Muscular Ventricular Septal Defect), 618

Procedural Details (Muscular Ventricular Septal Defect), 619

Complications, 620

Clinical Trial Data, 620

POST-MYOCARDIAL INFARCTION

VENTRICULAR SEPTAL DEFECT, 620

Management, 620

Transcatheter Post-Myocardial Infarction Ventricular Septal Defect Closure, 620

CONCLUSIONS, 622

PATENT FORAMEN OVALE

Introduction

In young adults, the prevalence of patent foramen ovale (PFO) is estimated at 34%, which drops to 20% in the eighth and ninth decades of life.¹ A potential causal relationship between PFO and stroke was first described by Cohnheim in 1877.² In the past 2 decades, several studies have investigated the role of PFO in cryptogenic ischemic stroke, migraine headaches, platypnea-orthodeoxia, and decompression sickness.³⁻⁵ Around 40% to 50% of patients with cryptogenic strokes are diagnosed with a PFO.⁶ Transcatheter PFO closure has emerged as a treatment option in the past 2 decades, with growing evidence around its indications. Results of several randomized trials of transcatheter PFO closure have been recently reported.

Developmental Anatomy of the Atrial Septum

During fetal life, there is a single atrial cavity (Figure 33.1). A septum primum (SP) develops from the atrial roof and

grows toward the endocardial cushions, thereby dividing the single atrium into left- and right-sided chambers. The area between the SP and the endocardial cushions is known as ostium primum (OP). Fenestrations then develop in the middle of the septum primum and coalesce to form ostium secundum (OS). The OS allows right-to-left shunting of oxygenated blood. To the right of septum primum, another septum known as the septum secundum (SS) then develops and covers the OS and in most instances covers the OP as well. A flaplike valve known as PFO is formed between the two septae, which now allows oxygenated placental blood to cross over from right-to-left atrium during the remainder of intrauterine life. Spontaneous fusion of SP with SS occurs in about 75% of the individuals by 2 years of age, leading to closure of PFO. In the remaining individuals, there is an oblique crescent-shaped defect resembling a tunnel, known as PFO.⁷ Some familial and genetic determinants have been implicated in the process of SP and SS fusion, but the mechanism of failure of spontaneous PFO closure has not been well understood.

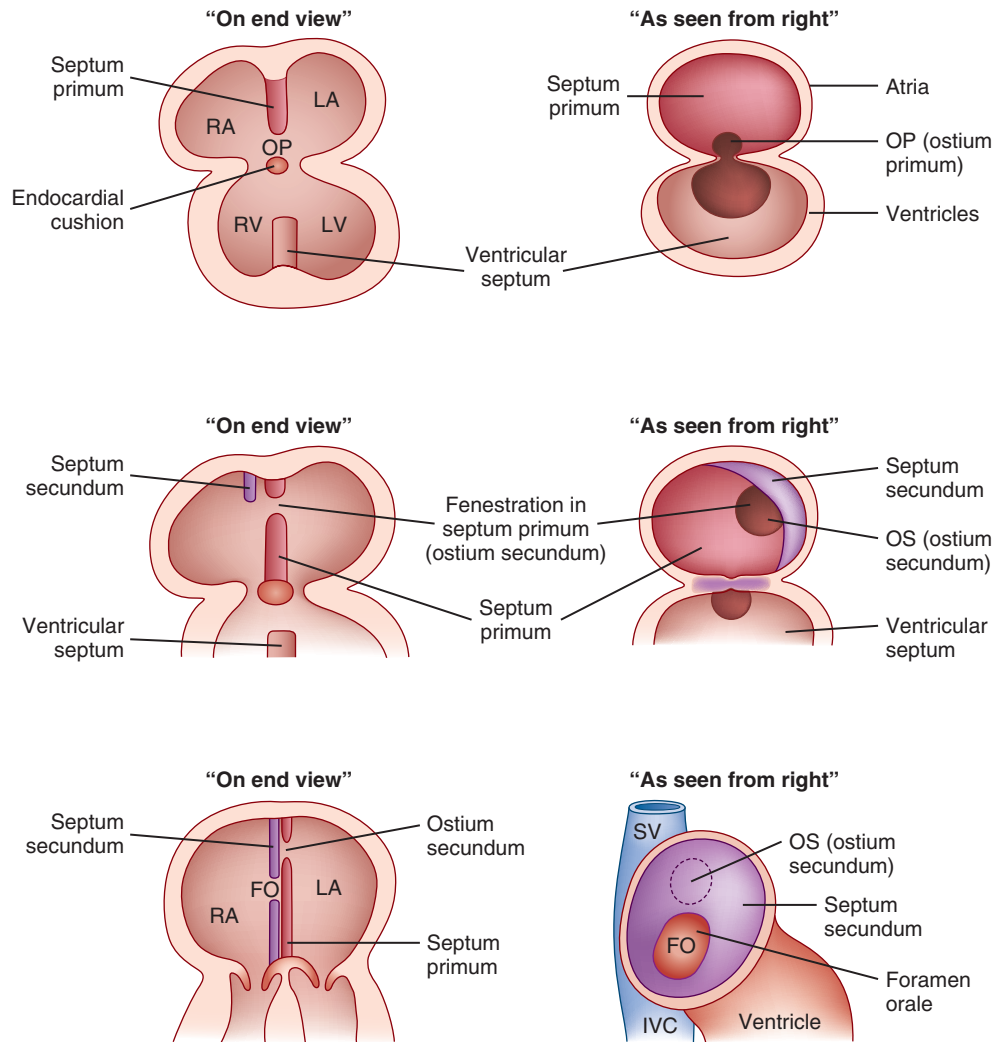


FIGURE 33.1 Development of the interatrial septum. FO, Foramen ovale; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; SV, superior vena cava.

Clinical Presentation

Paradoxical embolism of a thrombus originating in pelvic or lower extremity veins has been implicated as a mechanism to explain association between PFO and ischemic stroke. The incidence of pelvic deep vein thrombosis (DVT) has been found to be significantly higher in patients with cryptogenic stroke and PFO than in patients with stroke of determined origin.⁸ Paradoxical embolism requires at least a transient increase in pressure gradient between the right and left atria. Some PFOs have a long overlap between the SP and SS referred to as the tunnel. There are several reports of thrombus visualized “in transit” through PFO on transthoracic echocardiography (TTE) as well as transesophageal echocardiography (TEE) (Figure 33.2 and Video 33.1).^{9,10} This has also led to speculation that stagnated blood in the tunnel may lead to thrombus formation, which may subsequently embolize in the systemic circulation—an explanation often referred to as the “lurking clot theory.”¹¹ Studies have shown an association between the presence of atrial septal aneurysm (ASA) and risk of stroke.^{5,6,12}

Platypnea-orthodeoxia is a rare clinical syndrome characterized by dyspnea and oxygen desaturation in the

upright position that is relieved by lying down or recumbence. In the absence of elevated right-sided pressures, or lung disease, this can occur because of an anatomic abnormality that predisposes to right-to-left shunt from a PFO, such as a prominent eustachian valve that directs blood from the inferior vena cava (IVC) toward the interatrial septum, an aortic aneurysm, or an enlarged or elongated and horizontal aortic root that distorts the interatrial septum thereby predisposing to right-to-left shunting during upright position. TTE or TEE in the sitting position may be required to demonstrate flow across the septum by color or contrast if negative in supine position. Cardiac magnetic resonance imaging (MRI) or computed tomography (CT) may help demonstrate aortic abnormalities. Transcatheter PFO closure has been shown to be associated with marked improvement in symptoms.¹³

Decompression sickness occurs when a diver ascends from a dive and nitrogen bubbles entering venous circulation, which usually get diffused in the lungs, enter the systemic circulation via a right-to-left shunting source such as PFO and embolize to the brain, leading to ischemic lesions. A prospective study of 104 SCUBA divers with history of major decompression sickness showed that

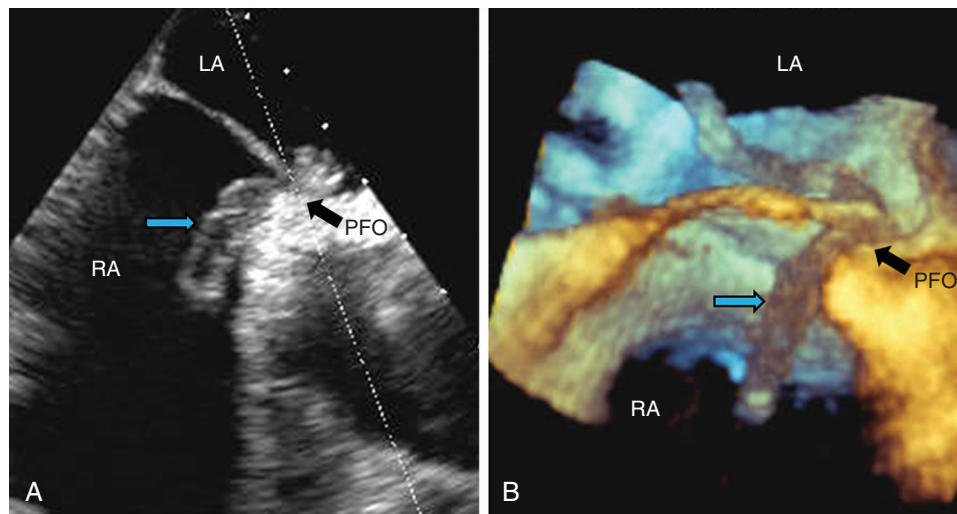


FIGURE 33.2 Thrombus (arrow) in transit visualized using two-dimensional (A) and three-dimensional (B) transesophageal echocardiography. LA, Left atrium; PFO, patent foramen ovale; RA, right atrium.

transcatheter PFO closure appears to prevent symptomatic and asymptomatic (ischemic brain lesions on MRI) decompression sickness.¹⁴

Migraine is a common disorder affecting about 10% of the adult population and is more common in women. In the past 2 decades, studies have shown an association between PFO and migraine, especially migraine with aura.¹⁵ Several retrospective observational studies have reported an improvement in migraine after PFO closure.^{16,17}

A significant reduction in the frequency and severity of migraine was demonstrated with PFO closure in patients with large PFO (based on transcranial Doppler [TCD]) and subclinical brain MRI lesions.¹⁸ These brain lesions may indicate silent thromboembolism, and these patients may be at high risk for future embolic events. Similarly, Rigatelli and colleagues¹⁹ recently showed that PFO closure resulted in a significant reduction in migraine in patients with high-risk PFO characteristics such as curtain shunt pattern on TCD and TEE (implying larger degrees of shunting), right-to-left shunting during normal respiration, ASA, and presence of eustachian valve.¹⁹

Not all patients with migraine have a PFO, and not all patients with PFO have migraine. The prospective trials evaluating role of PFO closure in migraine are discussed later. The onus is on future trials to identify patients who would benefit most from PFO closure based on high-risk PFO morphology, which is best assessed with TEE, and possibly also those with subclinical lesions on brain imaging.

Diagnosis

Patent foramen ovale can be detected using various echocardiographic techniques, including TTE, TEE, and TCD. More recently, three-dimensional echocardiography (3DE), CT, and MRI have been used, although none is the primary diagnostic tool in routine practice. Agitated saline is commonly used for diagnosing right-to-left shunts. Although the definition of positive contrast study result on TTE or TEE remains controversial, it is generally accepted that a right-to-left shunt is diagnosed if at least three microbubbles

appear in the left atrium, either spontaneously or after provocative maneuvers such as cough or Valsalva, within 3 cycles of complete opacification of the right atrium (Figure 33.3).⁵ A provocative maneuver increases right atrial (RA) filling, thus increasing the RA pressure and opening the foramen ovale. Valsalva maneuver can be calibrated (40 mm Hg of strain measured by spirometry and sustained for 10 seconds).²⁰ A good Valsalva maneuver is sometimes more difficult to obtain during TEE, especially if the patient is heavily sedated, compared with TTE or TCD. Some studies have shown that sensitivity of detection of PFO was increased when a femoral vein was used for contrast injection instead of the antecubital vein.^{21,22} This is likely because of different inflow pattern into the RA after injection through the femoral vein. Contrast through the IVC is directed toward the interatrial septum, often potentiated by a eustachian valve (see Figure 33.3), whereas contrast through the superior vena cava (SVC) is directed toward the tricuspid valve. Different morphologic characteristics of PFO such as size, degree of shunting, and tunnel length should be taken into account when evaluating a patient with PFO and cryptogenic stroke (see Figure 33.3).²³ TCD of the middle cerebral artery after injection of contrast can similarly be used to diagnose right-to-left shunting. Echocardiography can determine the magnitude of shunt, which is divided into grade 1, less than 5 bubbles; grade 2, 5 to 25 bubbles; grade 3, more than 25 bubbles; and grade 4, opacification of the entire chamber.²⁴

Transesophageal echocardiography has been shown to correlate very well with autopsy findings, with a sensitivity and specificity approaching 100% in the diagnosis of PFO.²⁵ Because of its high sensitivity and greater image resolution of the interatrial septal area allowing detailed characterization of PFO morphology, TEE is the current gold standard to diagnose and characterize PFO (see Figure 33.3). The drawbacks of TEE are its semi-invasiveness and occasional inability to obtain a good Valsalva maneuver in sedated patients.

Three-dimensional echocardiography using reconstruction techniques as well as real-time analysis have been

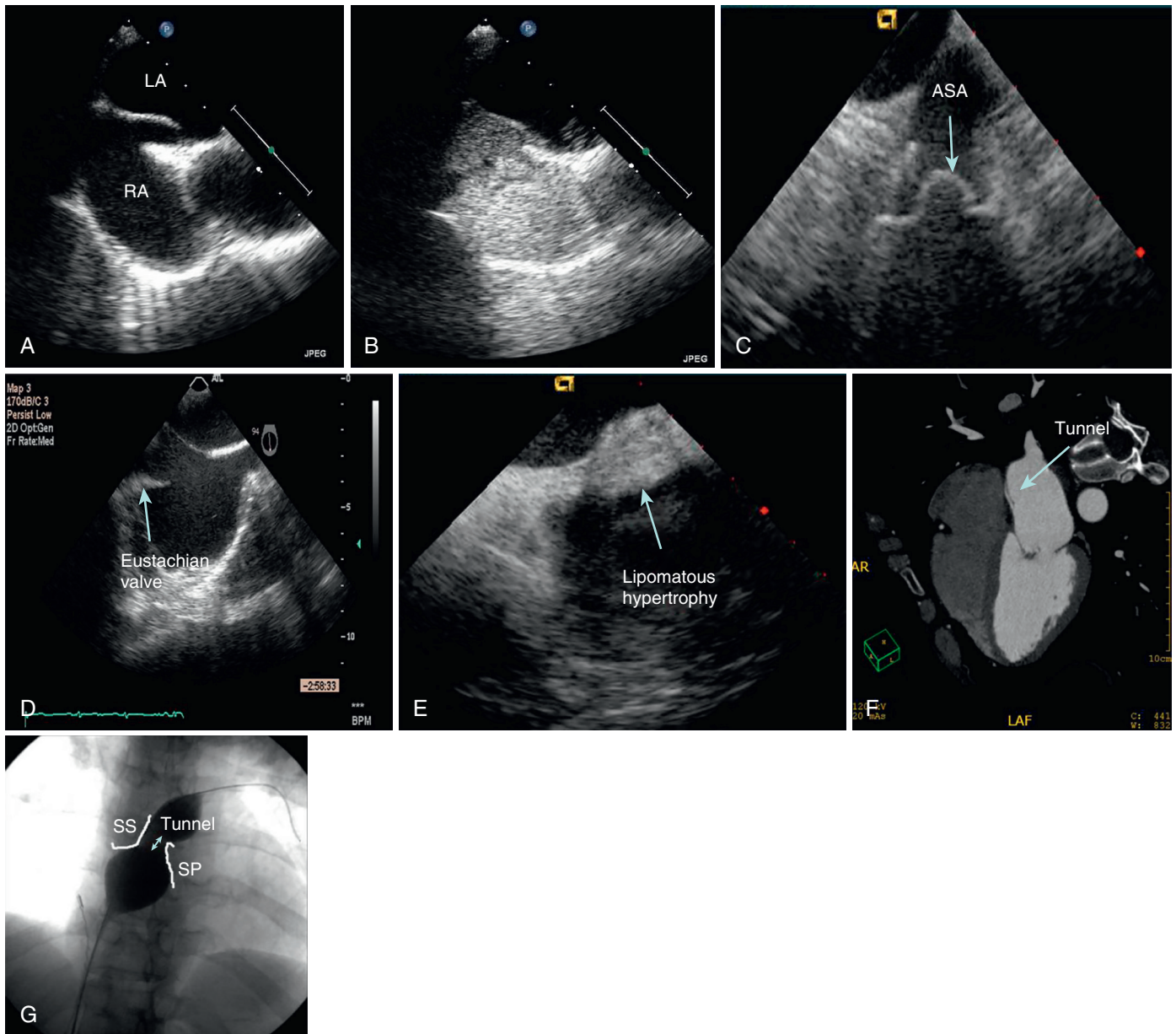


FIGURE 33.3 Diagnosis of patent foramen ovale (PFO) and associated morphologic features. **A**, PFO as visualized on transesophageal echocardiography. **B**, Positive bubble study on transesophageal echocardiography through PFO. **C**, Atrial septal aneurysm (ASA). **D**, Eustachian valve. **E**, Lipomatous hypertrophy of the interatrial septum. **F**, PFO tunnel as visualized on cardiac computed tomography. **G**, PFO tunnel with balloon occlusion during transcatheter closure on fluoroscopy. LA, Left atrium; SP, septum primum; SS, septum secundum.

used to evaluate a wide range of pathologies, including PFO. In a recent comparison, the diagnostic accuracy of real-time 3D TTE was significantly higher than that of contrast TTE: sensitivity 83% versus 44% ($P < .001$) and close to that of contrast TEE.²⁶

Small studies using contrast-enhanced MRI and cardiac CT (see Figure 33.3) have shown good concordance with TEE in the diagnosis of PFO. However, larger studies have shown both modalities to be inferior compared with TEE in detecting PFO.^{27,28}

Management

Currently, the best treatment for prevention of stroke in patients with PFO is becoming clearer with growing evidence in support of transcatheter PFO closure in certain

populations. There are data to suggest that PFO is more common in patients with cryptogenic stroke compared with those with a known cause of ischemic stroke.³ However, PFO is fairly common in the “control” population without stroke (prevalence, ~25%–34%), and there are many unknown causes of “cryptogenic stroke.” The available options include antiplatelet therapy, anticoagulant therapy, transcatheter closure, and surgical closure. It is very likely that not all PFOs are “culprits” responsible for pulmonary thromboembolism (PTE), especially because of the high prevalence of PFO in the general population. Supporting this, a meta-analysis showed that one-third of detected PFOs in patients with cryptogenic stroke are likely to be incidental and not benefit from closure, suggesting the importance of patient selection in therapeutic decision making.²⁹ Surgery is successful in PFO closure, but it is

very invasive and associated with significant morbidity.³⁰ Therefore, medical therapy and transcatheter PFO closure are the main therapeutic options. Recently, the Society of Cardiovascular Angiography and Interventions (SCAI) has issued a guideline document based on an expert panel review of available literature for management of PFO.³¹

Medical Therapy

At present, there is no consensus regarding antiplatelet versus anticoagulant therapy in patients with cryptogenic stroke and PFO, as reflected by the heterogeneity in the medical arms of the published randomized PFO closure trials. Data from the WARSS (Warfarin-Aspirin Recurrent Stroke Study) show that there was no difference between treatment with warfarin or aspirin in the prevention of recurrent ischemic stroke or death in a large cohort of patients with cryptogenic stroke.³² The PICSS (Patent Foramen Ovale in Cryptogenic Stroke Study), which is a substudy of WARSS with patients undergoing TEE examination, showed that there was a nonsignificant trend toward lower 2-year risk of stroke or death among warfarin-treated cryptogenic stroke patients with PFO compared with those receiving antiplatelet treatment (9.5% vs 17.9%; hazard ratio [HR], 0.52; confidence interval [CI], 0.16–1.67).³³ In the patent foramen ovale and atrial septal aneurysm study group (PFO-ASA) study, consisting of more than 580 patients with ischemic stroke of unknown origin, recurrent stroke occurred more commonly despite aspirin therapy in patients with PFO and ASA compared with those with PFO or ASA alone (HR for combination of PFO and ASA, 4.17; 95% CI, 1.47–11.84), suggesting that preventive strategies in addition to aspirin may be needed for such patients with high-risk PFO anatomy.⁵ A meta-analysis of retrospective studies also suggests benefit of anticoagulation over antiplatelet therapy for prevention of recurrent neurologic events in patients with PFO and cryptogenic stroke.³⁴ The recently published SCAI guidelines recommend transcatheter PFO closure over antiplatelet or anticoagulant therapy in patients with cryptogenic stroke and PFO based on data summarized later in this chapter.³¹

Transcatheter Patent Foramen Ovale Closure

Retrospective studies and meta-analyses have shown benefit associated with PFO closure in patients with cryptogenic stroke.^{31,34} However, the first three completed prospective randomized trials failed to show such benefit as detailed later. This suggests that the real-world selection of high-risk patients in whom PFO-related PTE is the cause of stroke may potentially be a beneficial approach. Subsequently, multiple randomized controlled trials (RCTs) demonstrated the benefit of transcatheter PFO closure in patients with high-risk anatomy, including ASAs and large shunts. In this perspective, the Risk of Paradoxical Embolism (RoPE) score was created to determine the likelihood of PFO-associated strokes and who would benefit the most from PFO closure. The score includes age, cortical infarction, lack of hypertension, diabetes, previous stroke or transient ischemic attack (TIA), and smoking status. A score of 7 or greater is in favor of PFO-associated

stroke. Additionally, the PFO-Associated Stroke Causal Likelihood (PASCAL) classification system combines the RoPE score with the presence or absence of high-risk PFO features such as ASA and large shunt to determine the likelihood that the PFO was causally related to the index stroke (unlikely, possible, or probable).³⁵ Next, we summarize the RCTs that led to such conclusions.³⁶

Randomized Trials of Patent Foramen Ovale Closure for Cryptogenic Stroke

In the first randomized, multicenter, open-label trial of transcatheter PFO closure, the CLOSURE 1 (Evaluation of the STARFlex Septal Closure System in Patients With Stroke and/or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a PFO) study, 909 patients with cryptogenic stroke or TIA between the age of 18 and 60 years were randomized to medical therapy or transcatheter PFO closure using the STARFlex device. With a success rate of 89% for closure, there was no difference in the outcomes of recurrent stroke at 2-year follow-up (2.9% vs 3.1%; $P = .79$) or TIA (3.1% vs 4.1%; $P = .44$) with closure compared with medical therapy.³⁷ In addition, there was a higher incidence of atrial fibrillation (AF) in patients in the device group (5.7% vs 0.7%; $P < .001$). There were many limitations of the CLOSURE 1 trial. The majority of recurrent events in this study (20 of 23 patients in closure group and 22 of 29 patients in medical therapy group) were not related to PTE, and alternative explanations for recurrent neurologic events were observed, including AF, subcortical lacunar infarcts, aortic arch atheroma, complex migraine, and vasculitis. This increases the likelihood that the initial neurologic event may not have been related to PFO and PTE. Thus, patients in the CLOSURE 1 trial may not have been the ideal population for study of PFO closure. Only one-third of patients in this trial had high-risk features such as ASA, and only about a half had significant shunting. Closure of insignificant or incidental PFOs may have diluted the beneficial effects of PFO closure. Patients with hypercoagulable testing or DVT were excluded from this study, thus excluding patients in whom the mechanism of stroke was perhaps most likely to be related to PTE. Moreover, even though the CLOSURE trial is being viewed as a “negative” trial, it shows that PFO closure is an effective alternative to medical therapy in reducing stroke.

In RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment), a randomized, multicenter, open-label trial, 980 patients between the age of 18 and 60 years with cryptogenic stroke were randomized to medical therapy or transcatheter PFO closure.³⁸ In the intention-to-treat cohort, recurrent stroke occurred in 9 patients in the closure group and 16 in the medical therapy group (HR with closure, 0.49; 95% CI, 0.22–1.11; $P = .08$). In contrast, there was statistically significant reduction in the risk of recurrent stroke with PFO closure when analyses were performed in prespecified per-protocol cohort (HR, 0.37; 95% CI, 0.14–0.96; $P = .03$) and as-treated cohort (HR, 0.27; 95% CI, 0.10–0.75; $P = .007$). In addition, closure was found to provide greater benefit in patients with severe right-to-left shunt and in those with an ASA.

Strengths of the RESPECT trial over CLOSURE 1 trial include longer follow-up; more stringent inclusion criteria with exclusion of patients with TIA and lacunar infarcts; and use of the Amplatzer PFO Occluder device, which provides more effective closure rates with lower device-related complications such as thrombosis and AF. Limitations of the RESPECT trial include high dropout rate (17% in medical therapy group and 9% in closure group) and nonadherence to protocol in some patients with important implications on outcomes (3 of 9 patients with recurrent ischemic stroke in the closure group of the intention-to-treat population did not have a device at the time of recurrent stroke). Subsequently, an extended follow-up of the RESPECT trial, with a median of 5.9 years, showed continued benefit in the device group with a 62% relative risk (RR) reduction in stroke.³⁹

In the PC (Comparing Percutaneous closure of PFO using the Amplatzer PFO Occluder with medical treatment in patients with cryptogenic embolism) trial, 414 patients were randomized to transcatheter PFO closure or medical therapy.⁴⁰ Recurrent stroke occurred less frequently in the closure group than in the medical therapy group; however, this was not statistically significant (0.5% vs 2.4%; HR, 0.20; 95% CI, 0.02–1.72; $P = .14$). Closure also did not reduce recurrent TIAs compared with medical therapy alone (2.5% vs 3.3%; HR, 0.71; 95% CI, 0.23–2.24; $P = .56$). Limitations of the PC trial include inclusion of TIA in the primary endpoint and difficulty recruiting patients with a long recruitment period.

In CLOSE (Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke), a randomized, multicenter, open-label trial, 663 patients with recent stroke attributed to a high-risk PFO (ASA or large interatrial shunt) between the age of 18 and 60 years were randomized to PFO closure versus antiplatelet therapy versus anticoagulation (1:1:1 ratio).⁴¹ At 5.3 years of follow-up, the PFO closure group had less stroke recurrence (0 vs 6%, HR 0.03; 95% CI, 0–0.26; $P < .001$) compared with the antiplatelet group with no significant difference in serious adverse events. There was a significant increase in AF in the procedural group (4.6% vs 0.9%, $P = .02$), which mainly occurred in the first month after than procedure (91%) and had no recurrence over the study period.

The Gore REDUCE (Gore Helex Septal Occluder/Gore CARDIOFORM Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale) is a randomized, multicenter, open-label trial that compared the Gore Helex occluder and CARDIOFORM septal occluder (GCSO; WL Gore and Associates) with medical therapy in patients with recent cryptogenic stroke between the age of 18 and 60 years.⁴² Patients were randomized in a 2:1 ratio to transcatheter PFO closure versus antiplatelet therapy. The patients underwent a multitude of testing to determine whether other causes of stroke (e.g., AF, carotid atherosclerosis, lacunar infarcts) were causative of their prior episode. In addition, patients with significant cardiovascular risk factors were excluded from the trial. During the follow-up period (median, 3.2 years), the invasive group had less recurrence of ischemic stroke than the medical group (1.4% vs 5.4%; HR, 0.23, 95% CI, 0.09–0.62; $P = .002$) without a significant increase in serious adverse events. AF occurred more frequently in the closure group (6.6% vs 0.4%; $P < .001$), with a predominance in the first 45 days (83%) after the procedure.

The DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale) trial enrolled 120 patients with recent cryptogenic ischemic stroke and high-risk PFO to either transcatheter PFO closure using the Amplatzer PFO Occluder or medical therapy.⁴³ High-risk PFO was defined as PFO with ASA, hypermobility (septal excursion ≥ 10 mm), or size 2 mm or larger. Similar to the REDUCE trial, patients were thoroughly evaluated for other causes of stroke using CT angiography, magnetic resonance angiography, or ultrasonography, Holter monitoring, and TEE. At 2 years of follow-up, the primary endpoint (composite of stroke, vascular death, or TIMI [Thrombolysis in Myocardial Infarction]-defined major bleeding) occurred in 12.9% of the medical group versus 0% of the PFO closure group ($P = .013$). The closure group had no ischemic stroke, vascular death, major bleeding, hemorrhagic stroke, TIA, or systemic embolism. There was no significant difference in the new ischemic lesions detected by MRI in both groups (8.8% vs 18.4%, $P = .24$). Two patients developed AF after transcatheter PFO closure.

A meta-analysis that included all the studies described demonstrated that recurrent stroke was less frequent in the PFO closure group compared with the medical therapy group.⁴⁴

Patent foramen ovale closure is mostly beneficial in patients with high-risk PFO features (ASAs or large shunt) compared with lower risk PFO patients (RR = .27, 95% CI, 0.11–0.70; $I^2 = 42\%$). In a recent individual participant data meta-analysis that included six randomized clinical trials with 3740 patients with cryptogenic stroke and PFO, subgroup analyses using the RoPE score and the PASCAL classification system were performed to explore heterogeneity of treatment effect.⁴⁵ Over a median follow-up period of 57 months, the annualized incidence of stroke with medical therapy alone was 1.09% (95% CI, 0.88%–1.36%) and with transcatheter PFO closure was 0.47% (95% CI, 0.35%–0.65%) (adjusted HR, 0.41; 95% CI, 0.28–0.60). Subgroup analyses showed significant interaction effects. For patients classified as unlikely (i.e., with vascular risk factors [low RoPE score] and without high-risk PFO features), the HR was 1.14; for those classified as possible (high RoPE or high-risk PFO features) or probable (high RoPE and high-risk PFO features), the HRs were 0.38 and 0.10, respectively. In other words, PFO closure is associated with the most benefit in patients with the highest probability that the index stroke was causally related to the PFO. This classification can potentially help guide individualized decision-making processes in patients with cryptogenic stroke and PFO.

Indications for Transcatheter Patent Foramen Ovale Closure

Stroke

After the PC and RESPECT trials, the Amplatzer PFO Occluder was approved by the US Food and Drug Administration (FDA) in October 2016 for treatment of PFO-associated stroke in patients between the age of 18 and 60 years. The 2021 American Heart Association (AHA)/ACC guidelines recommend a multidisciplinary team approach (cardiologist and neurologist) for the management of patients with

nonlacunar ischemic stroke (Class of Recommendation [COR] 1, Level of Evidence [LOE] C). In addition, it is reasonable to choose transcatheter PFO closure over medical therapy alone in patients with a high-risk PFO anatomy (ASA or large shunt) (COR 2a, LOE B-R). Finally, it is unclear whether transcatheter PFO closure is more beneficial than medical therapy for patients with a low-risk PFO anatomy (COR 2b, LOE C).⁴⁶

Migraine

The MIST (Migraine Intervention with STARFLEX Technology) trial was a prospective, randomized, double-blind trial in patients undergoing PFO closure primarily for migraine control that failed to show any significant difference of PFO closure on the primary endpoint of migraine cessation or secondary endpoints of improvement in migraine compared with a sham procedure.⁴⁷ However, the MIST trial was found to have several limitations, including an unrealistic endpoint of migraine cessation, inadequacy of TTE in screening for PFO as indicated by the absence of PFO during closure, and a shorter duration of follow-up. The PREMIUM (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management) trial studied percutaneous closure (117 patients) versus sham procedure (103 patients undergoing a right heart catheterization) in patients who failed three preventive migraine medications.⁴⁸ There was no difference in the primary endpoint, which was a 50% reduction in migraine attacks and adverse events. On the other hand, there was a reduction in headache days with PFO closure (-3.4 vs -2.0 days/month; $P = 0.025$), and complete remission at 1 year occurred more frequently in the closure group (8.5% vs 1%, $P = .01$). It is important to note that these patients were suffering from refractory migraines. The PRIMA (Percutaneous closure of patent foramen ovale in Migraine with Aura, an RCT) trial was a multicenter trial that randomized 107 patients with migraine with aura to closure with Amplatzer PFO Occluder ($n = 53$) versus medical therapy ($n = 54$).⁴⁹ Because of slow enrollment, only 83 patients had 12-months follow-up (intervention group, 40; control group, 43). There was no decrease in the number of migraine days (8 ± 4.7 days vs 8.3 ± 2.4 days). Subsequently, a meta-analysis involving the two studies (PRIMA and PREMIUM trials) demonstrated several endpoints in favor of the PFO closure group, including mean reduction of migraine days per month (-3.1 days vs -1.9 days; $P = .02$) and number of patients who had complete cessation of migraine (9% vs 0.7%; $P < .001$).⁵⁰

Off-label PFO closure has been performed in patients with paradoxical embolic events presumed to be related to PFO, platypnea-orthodeoxia syndrome, decompression sickness, and migraine headaches. The most recent SCAI guidelines recommend against the routine use of PFO closure in patients with migraine or prior decompression illness; however, they provide conditional recommendation acknowledging the low certainty of evidence in support of closure for platypnea-orthodeoxia syndrome when other causes of hypoxia have been excluded and in the setting of systemic embolism without prior PFO-associated stroke when other embolic causes have been excluded.³¹

Devices

Currently, the Amplatzer PFO Occluder (Abbott) and GCSO are approved for transcatheter PFO closure in the United States. Transcatheter PFO closure has also been performed with devices that are used for transcatheter atrial septal defect (ASD) closure (Figure 33.4). These include the Amplatzer atrial septal Occluder (ASO) (Abbott) and Amplatzer multifenestrated, or cribriform ASO. In addition, the CardioSEAL, STARFlex, Helex, and Premere PFO closure systems were also used in the past.

Amplatzer Devices

The Amplatzer PFO Occluder, used in the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT), Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism (PC), and Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale (DEFENSE PFO) trials, is a self-expanding, double-disk device made of 0.005-inch nitinol wire and polyester patches sewn within each disk to occlude blood flow (see Figure 33.4). The waist is thin and mobile, and the RA disk is larger than the left atrial (LA) disk, in contrast to the Amplatzer ASO device. The device was approved for PFO closure by the FDA on October 28, 2016. There are three device sizes available, based on the RA disk diameter—18, 25, and 35 mm. Device sizing depends on distance from the PFO to the SVC or aorta. The 25-mm device is used in the majority of cases. The Amplatzer cribriform ASO device, used for closure of fenestrated secundum ASDs, also has been used for PFO closure. It consists of a thin waist and equal-sized left and RA disks and is available in four sizes—18, 25, 30, and 35 mm. The Amplatzer ASO device is discussed in the ASD closure section.

GORE CARDIOFORM Septal Occluder

The GCSO (see Figure 33.4), which was approved by the FDA for PFO closure on March 30, 2018, has replaced the previous Helex device. Similar to the Helex device, it is a platinum-filled nitinol wire frame covered with expanded polytetrafluoroethylene (PTFE). The delivery system is composed of a 10-Fr (Outer Diameter [OD]) 75-cm braided, precurved delivery catheter with a radiopaque distal marker. The device has a central and LA and RA eyelets. Each eyelet is composed of five petals to cover the septal wall. The device is repositionable and retrievable. The device is available in diameters of 20, 25, and 30 mm.

Procedural Details

Transcatheter PFO closure is performed in the cardiac catheterization laboratory under conscious sedation (the authors use midazolam and fentanyl) with fluoroscopic and ultrasound guidance (TEE, or now usually intracardiac echocardiography [ICE]) (Figure 33.5 and Video 33.2). Single-side femoral venous access is obtained in the right femoral vein with an 11-Fr sheath above for the device and a 9-Fr, 35-cm sheath below for ICE catheter. Both venous access points are preclosed with a ProGlide device. The ICE catheter is advanced into the right atrium, the interatrial septum is adequately interrogated, and bubble study

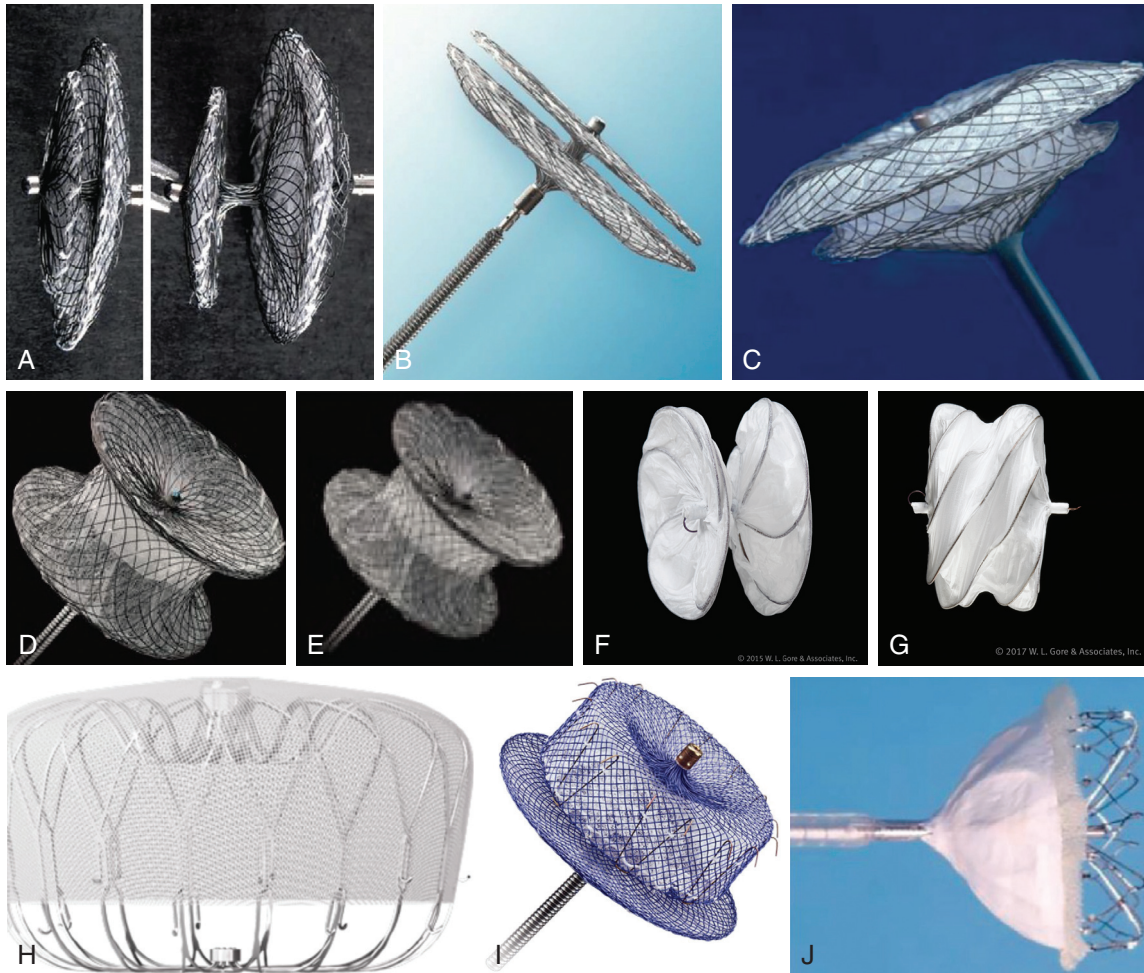


FIGURE 33.4 Devices for transcatheter closure of patent foramen ovale (PFO), atrial septal defect (ASD), left atrial appendage (LAA), and ventricular septal defect (VSD) closure discussed in this chapter. **A**, Amplatzer PFO Occluder. **B**, Amplatzer multifenestrated “cribriform” occluder. **C**, Amplatzer septal Occluder. **D**, Amplatzer muscular VSD Occluder. **E**, Amplatzer post-myocardial infarction VSD Occluder. **F**, Gore CARDIOFORM septal Occluder. **G**, Gore CARDIOFORM ASD Occluder. **H**, Watchman FLX LAA Occluder. **I**, Amulet device. **J**, Coherex WaveCrest device. Amplatzer, Amplatzer Amulet and Amulet are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, © 2023. All rights reserved.

is performed through the contralateral femoral venous sheath. A multipurpose catheter is advanced with a 0.035-inch J-tipped guidewire into the SVC. The guidewire is removed, and the catheter is connected to the manifold. RA angiography can then be performed if needed. The catheter is then directed toward the interatrial septum, and the PFO is crossed with or without the 0.035-inch J-tipped guidewire using ICE and fluoroscopic guidance. When across the PFO, intravenous heparin is administered to achieve an activated clotting time (ACT) above 200 to 250 seconds. The catheter and guidewire are placed in the left superior pulmonary vein, with care taken to ensure that the wire tip is not in the left atrial appendage (LAA) to avoid perforation. The 0.035-inch J-tipped guidewire is exchanged for a 0.035-inch J-tipped Amplatzer extra-stiff wire, again taking care to ensure that the tip is not in the appendage. The PFO diameter is then measured with a sizing balloon, with care taken to inflate the balloon gently to avoid tearing the interatrial septum. The next steps depend on the device used.

For the GCSO device, the system is prepped and flushed as recommended by the manufacturer. A device to

balloon-stretched diameter of at least 1.75:1 is recommended. A 10-Fr sheath without a guidewire or a 12-Fr sheath with a guidewire is used. After initial prepping, the delivery catheter is placed in the left atrium over the 0.035-inch extra-stiff guidewire. The guidewire is removed, and the LA disk is deployed under fluoroscopic and ICE guidance to ensure positioning in the left atrium away from the roof and appendage (see [Figure 33.5](#)). The entire system is then pulled against the left side of the interatrial septum. The RA disk is then deployed. Placement and positioning are confirmed with ICE and left anterior oblique (LAO) cranial projection on fluoroscopy, with the RA and LA disks straddling the septum (see [Figure 33.5](#)). After acceptable placement is confirmed, the occluder is locked, and the locking loop is best visualized in the right anterior oblique cranial projection. The retrieval cord lock is then pulled, disengaged from the slider and gently pulled until it is completely removed from the handle, and the device is deployed. The device can be reloaded before locking the occluder if appropriate position is not achieved. It can also be retrieved with the retrieval cord after locking but not after the retrieval cord is removed.

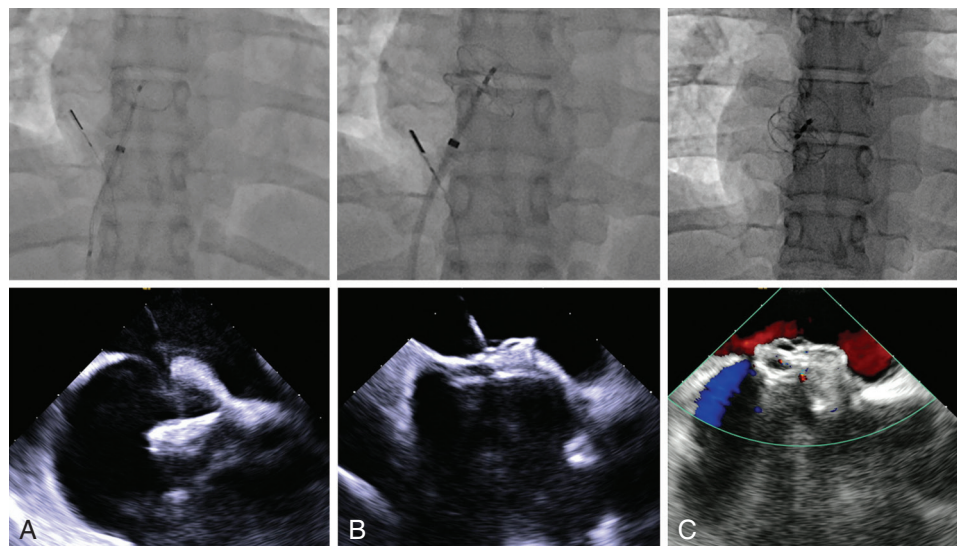


FIGURE 33.5 Intracardiac echocardiography and fluoroscopic images during transcatheter patent foramen ovale closure using the Gore CARDIOFORM Septal Occluder device. **A**, Gore device with left eyelet deployment. **B**, Deployment of the right eyelet of the device. **C**, Final device position after release.

For Amplatzer devices, the initial steps are similar to the GCSO. The device is loaded on the delivery cable and prepped as per the manufacturer's instructions to ensure no air in the system. The device is then introduced from the loader into the delivery sheath, which is placed in the mid left atrium and carefully pushed under fluoroscopy to ensure absence of air bubbles. When the device reaches the tip of the delivery sheath, the sheath is withdrawn gently, exposing the LA disk, under fluoroscopic and ICE guidance. After making sure there is adequate opening of the LA disk in the left atrium, the system is pulled against the LA side of the interatrial septum such that the LA disk abuts the septum. The sheath is then withdrawn, exposing the RA disk on the RA side under fluoroscopic and ICE guidance. After the device position is confirmed with fluoroscopy and ICE and felt to be stable and fully expanded without obstruction or impingement of nearby structures, the device is released. Femoral venous sheaths are removed, and hemostasis achieved by manual compression.

Postprocedure Care

It is our practice to administer two doses of antibiotics 12 hours apart. Patients are monitored with telemetry overnight and chest radiography and TTE with bubble study are performed the following morning to confirm accurate positioning. In the REDUCE trial, most patients received aspirin alone (81–325 mg/day); alternatively, aspirin (50–100 mg/day) and dipyridamole (225–400 mg/day) or clopidogrel (75 mg/day) were administered. TTE with bubble study is repeated at 6 months. Endocarditis prophylaxis is advised for 6 months.

Complications

Transcatheter PFO closure is a safe procedure; however, complications can occur in 1% to 4% of patients, with most complications being mild.^{34,38,40,42} The most frequent

reported complication after PFO closure is the occurrence of atrial arrhythmias, including AF and atrial flutter. In retrospective studies, new AF was observed in 3.9% of patients,³⁴ but the rate of AF was very low in the RESPECT trial (0.2%) compared with 4.6% and 6.6% in CLOSE and REDUCE trials, respectively. In a meta-analysis, transcatheter PFO closure was associated with an increased risk of AF or atrial flutter with an RR of 4.55 (.16–9.60).⁵¹ Device thrombosis occurs in 0.6% patients,³⁴ and device embolization can occur in 0.07% of patients.⁵² Device fracture was observed in older-generation devices but is extremely rare with the current devices. Serious bleeding from vascular complications occurred in 0.5% or fewer patients in the RESPECT and PC trials. Pericardial effusion or tamponade has been reported in 0.3% of patients.^{34,38} Device erosion has been reported with the Amplatzer septal Occluder, used for ASD closure, and generally believed to not be a risk with Gore devices, although case reports have documented in association with wire frame fracture with the Helix septal Occluder and the GCSO.⁵³ Air embolism is a potentially disastrous complication that can occur because of inadequate flushing of the device systems or the device systems are introduced into the delivery sheath. This complication can be easily avoided by careful flushing and paying meticulous attention to fluoroscopy while advancing the device through the delivery sheath.

ATRIAL SEPTAL DEFECT CLOSURE

Introduction

Atrial septal defect is the most common congenital heart defect presenting in adults after bicuspid aortic valve and accounts for 6% to 10% of all defects at birth. It affects twice as many females as males. Left-to-right shunting at the atrial level with right-sided volume overload and eventually pulmonary vascular disease and pulmonary hypertension are responsible for the clinical presentation. Since

FDA approval of a device for transcatheter ASD closure in December 2001, there has been a shift from surgical closure to transcatheter closure with excellent results and good prognosis in treated patients.

Anatomy

The development of the interatrial septum was discussed in the section on PFO (see [Figure 33.1](#)). There are four types of ASDs depending on location. The most common is secundum ASD (75% of all ASDs), which is a defect in the region of the fossa ovalis. The primum ASD (15%–20%) is located in the inferior portion of the atrial septum near the crux of the heart and occurs because of deficiency of endocardial cushion tissue. It is often associated with a cleft in the anterior mitral valve leaflet or ventricular septal defect (VSD) (common atrioventricular canal defects). The sinus venosus type of ASD (5%–10%) is located in the superior or inferior part of the septum near the entrance of the superior or IVC into the right atrium or SVC. The superior sinus venosus ASD is often associated with anomalous pulmonary venous drainage into the right atrium. Coronary sinus septal defect (<1%) is located in the wall separating the ostium of the coronary sinus from the left atrium. Only the secundum ASDs can be repaired by transcatheter closure; the other types require surgical closure. ASDs are associated with Down syndrome (particularly OP ASD), Holt-Oram syndrome, and DiGeorge syndrome. In addition, other associated lesions with ASD can include mitral valve prolapse and valvular pulmonic stenosis.

Pathophysiology

Atrial septal defect leads to shunting at the atrial level. The magnitude and direction of shunting depend on the defect size and the relative compliance of the ventricles. Usually the shunt is from the left to right atrium because of higher compliance of the right ventricle. With increasing age, the left ventricular (LV) compliance decreases and LA pressure rises, and the magnitude of left-to-right shunt increases. This leads to volume overload and enlargement of the right atrium, right ventricle, and pulmonary artery. Over time, high pulmonary blood flow occurring for several years leads to pulmonary vascular bed remodeling, an increase in pulmonary vascular resistance (PVR), and pulmonary hypertension. Left untreated, pulmonary vascular changes become irreversible, leading to severe pulmonary hypertension, right-sided pressure overload, and reversal of shunting, leading to right-to-left shunting.

Clinical Presentation

During childhood, patients with ASD are usually asymptomatic and may have a pulmonary outflow murmur or fixed splitting of the second heart sound detected incidentally during routine examination. Some children may present with recurrent respiratory infections or even heart failure. Typically, most young adults have a prolonged asymptomatic course. With increasing age, symptoms of reduced exercise tolerance, progressive exertional dyspnea, and heart failure occur with progressive left-to-right shunting as a

result of decreased LV compliance and increased LA pressure. Arrhythmias, including supraventricular arrhythmias, AF, or atrial flutter, may be the presenting sign. Paradoxical embolism resulting in stroke or ischemia of other organ systems may also occur. Untreated ASDs can lead to pulmonary vascular disease, pulmonary hypertension, and Eisenmenger syndrome in the absence of other causes, but typically not until adulthood.

Diagnosis

Physical examination findings that lead to evaluation for ASD include right ventricular (RV) heave, wide and fixed split of the second heart sound (caused by delayed pulmonary valve closure), ejection systolic murmur best heard at the left sternal border (reflecting increased blood flow through the pulmonary valve), and loud pulmonic component of second heart sound in patients with pulmonary hypertension. Ostium primum ASDs may have associated mitral and tricuspid regurgitation murmurs. Electrocardiographic findings include RA enlargement (P-pulmonale), right-axis deviation, RV hypertrophy (tall R wave in V1), and incomplete right bundle branch block (rSR' or rsR' in leads V1–V3) in secundum ASD. In primum ASD, left-axis deviation may be seen. First-degree atrioventricular block can be seen in any kind of ASD. Chest radiography findings include RA and RV enlargement, dilated pulmonary artery, and increased pulmonary plethora.

Echocardiography is the diagnostic modality of choice for ASD ([Figure 33.6](#)). In children, TTE provides most of the information; however, in adults, TEE is important for complete evaluation. The defect is usually seen on TTE from subcostal view of the interatrial septum or apical four-chamber view. Septal dropout is an important limitation of TTE, which can lead to false-positive diagnosis of ASD. Saline contrast echocardiography leads to accurate diagnosis in most cases. In addition to making a diagnosis, TTE demonstrates the presence of RA and RV enlargement and enables assessment of pulmonary artery pressure (PAP) using the tricuspid regurgitation jet velocity. The magnitude of left-to-right shunt using noninvasive calculation of pulmonary to systemic blood flow ratio (Qp/Qs ratio) can also be assessed but is rarely used because of inaccuracies. Additionally, TTE allows evaluation for other associated congenital anomalies such as pulmonary valve disease, mitral valve prolapse, and pulmonary venous drainage. Before transcatheter ASD closure, complete assessment using TEE or ICE (usually performed just before closure) is critical (see [Figure 33.6](#)). This allows assessment of various rims or margins for suitability for device closure; drainage of all four pulmonary veins; exclusion of sinus venosus-type ASDs, which can be missed by TTE; and detailed evaluation of mitral valve disease if present. Recently, 3DE has also been used for evaluating ASDs (see [Figure 33.6](#)). MRI is another noninvasive imaging modality that can be used if echocardiography does not provide all required information. MRI enables direct visualization of the defect and pulmonary venous drainage, calculation of shunt size, and quantification of RV volume and function. Contrast-enhanced cardiac CT can also provide similar anatomic information.

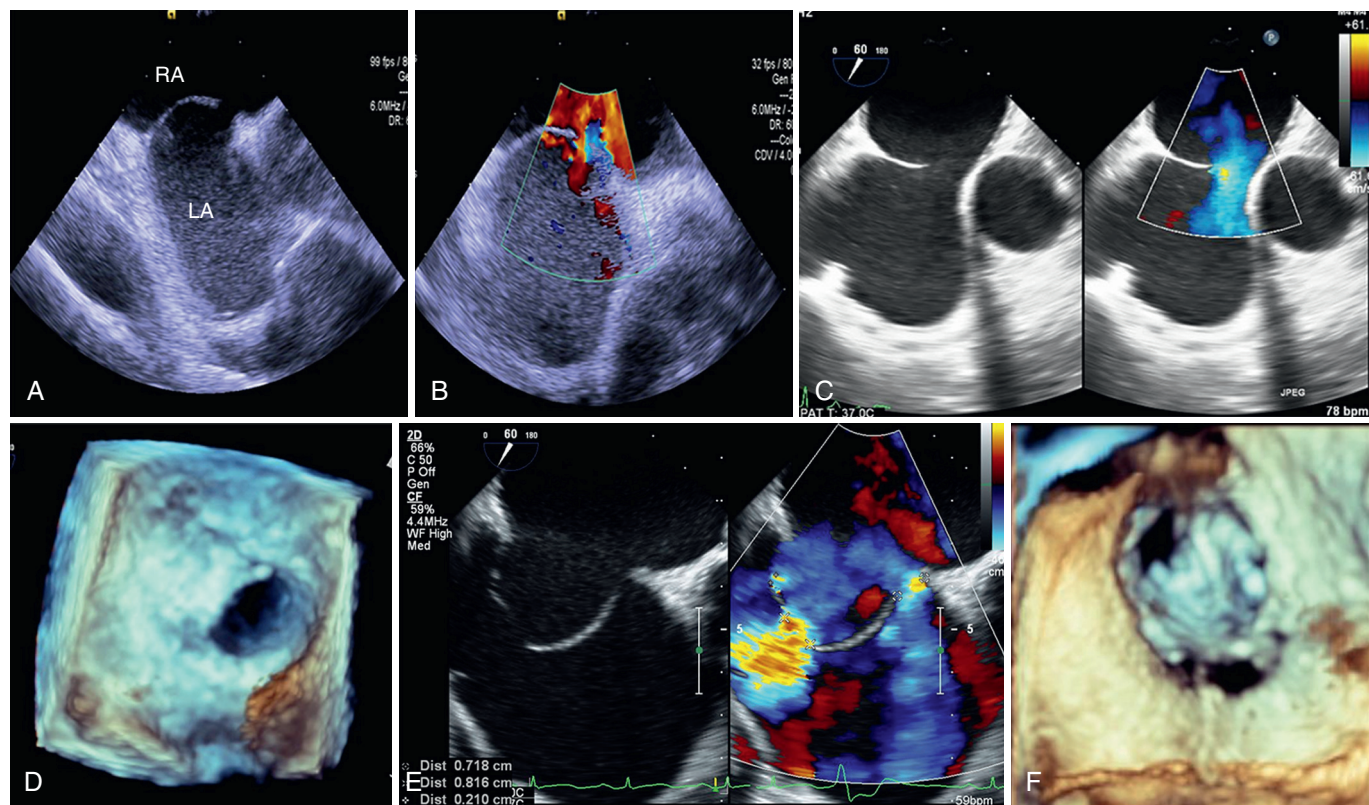


FIGURE 33.6 Diagnosis of atrial septal defect (ASD) by echocardiography. **A**, Secundum ASD as visualized by intracardiac echocardiography (ICE). **B**, Secundum ASD by ICE with color Doppler. **C**, Secundum ASD on transesophageal echocardiography with deficient anterior rim. **D**, Secundum ASD as visualized by three-dimensional echocardiography (3DE). **E**, Aneurysmal septum with cribriform ASD. **F**, Cribriform ASD on 3DE.

Cardiac Catheterization

In the current era, cardiac catheterization is not required to establish a diagnosis in the presence of adequate noninvasive imaging. Right heart catheterization with measurement of oxygen saturations (shunt run) and measurement of PAP and coronary angiography in patients older than 40 years of age are usually performed at the time of planned transcatheter closure. At the time of closure, pulmonary angiography can be performed to confirm the absence of anomalous pulmonary venous drainage; however, this is usually established by noninvasive imaging. Invasive hemodynamic assessment to determine shunt size may be needed when the hemodynamic significance is not clear by echocardiography and when there is the need to determine PVR and pulmonary vascular reactivity in the presence of pulmonary hypertension.

Management and Indications for Atrial Septal Defect Closure

Small ASDs with diameters smaller than 5 mm and no evidence of RV volume overload may not require closure because they do not usually impact the natural history. Unrepaired ASDs with significant shunting can result in right-sided volume overload, with progressive heart failure, arrhythmias, hemodynamically significant tricuspid regurgitation, pulmonary hypertension, Eisenmenger syndrome, and reduced survival. Current American College of Cardiology (ACC)/AHA guidelines recommend (Class I) ASD closure in the presence of a large shunt

(Qp/Qs ratio ≥ 1.5) and right-sided volume overload, that is, RV or RA dilation in a symptomatic or asymptomatic patient, provided that the pulmonary artery systolic pressure is less than 50% of the systemic pressure and the PVR is less than one-third of the systemic vascular resistance.⁵⁴ Closure in the presence of symptoms or right-sided heart enlargement prevents further deterioration and helps normalize the right-sided dilation. Natural history studies of ASD closure show reduced survival after closure in patients older than 24 years of age or with pulmonary hypertension (systolic PAP ≥ 40 mm Hg).⁵⁵ Additionally, closure in patients older than 40 years of age, although improving symptoms and mortality rates compared with a medically managed group, did not reduce the risk of atrial arrhythmias.⁵⁶ Therefore, ASD closure should be performed in a timely fashion in appropriate patients to prevent long-term complications. An ASD other than secundum ASD should be repaired surgically. Closure of ASD may be considered in some patients regardless of evidence of right-sided enlargement, for example, in professional divers and patients undergoing pacemaker implantation because of the risk of paradoxical embolism. Similarly, ASD closure may be considered before pregnancy. In patients with pulmonary arterial hypertension (PAH), pulmonary vasodilator testing to assess for reversibility and test occlusion of ASD should be performed. Inhaled nitric oxide is used commonly as a pulmonary vasodilator. A positive vasoreactivity response is defined as a reduction of mean PAP greater than 10 mm Hg with resultant mean PAP of 40 mm Hg or less without a decrease in cardiac output. Closure in such patients may

be performed if there is net left-to-right shunting, PAP is less than two-thirds systemic levels, or PVR is less than two-thirds SVR or when responsive to either pulmonary vasodilator testing or test occlusion. A favorable response is indicated by a decrease in mean PAP with test occlusion with no decrease in cardiac output and no increase in RA pressure. In the presence of unfavorable response, pulmonary vasodilator therapy should be initiated and hemodynamics reassessed a few months later. ASD closure is also indicated in the presence of paradoxical embolism and documented platypnea-orthodeoxia. An absolute contraindication (Class III) for closure is irreversible PAH and no evidence of left-to-right shunt.

Devices for Atrial Septal Defect Closure

Transcatheter closure has largely replaced surgical closure for a vast majority of cases of secundum ASDs with appropriate morphology in the absence of any other associated defects because of good outcomes and low rates of complications. The three devices approved by the US FDA for transcatheter ASD closure are the Amplatzer ASO (Figure 33.7), GCSO (WL Gore and Associates), and Gore CARDIOFORM ASD Occluder (WL Gore and Associates). Several other devices have received Conformité Européenne (CE) Mark in Europe but are currently unavailable in the United States. The Amplatzer ASO is a self-expandable, double-disk device made of nitinol wire mesh that is tightly woven into two disks with a 3- to 4-mm connecting waist between the two disks (see Figure 33.4). The superelastic properties of nitinol allow the device to be stretched and delivered via sheath size of 6 to 8 Fr. The device size is determined by the waist diameter and ranges from 4 to 40 mm (4–20 mm at 1-mm increments, 22–40 mm at 2-mm increments; the 40-mm device is not available in the United States). The disk diameters increase with increasing size, and the LA disk is 4 to 6 mm larger than the RA disk depending on device size because shunting is from left to right. The Amplatzer delivery system supplied separately from the device consists of a loader, hemostasis valve with extension tube and stopcock, delivery sheath of varying size and length (depending on device size to be used), a

dilator, and a delivery cable. All delivery sheaths have a 45-degree tip (45-degree TorqVue Delivery Sheath). There are sheaths with 180-degree turn available, but they are typically not used for ASD closure. A 60-degree angulated Hausdorf Sheath (Cook Medical) can be used for ASD with poor posterior inferior rim.

The GCSO is described earlier in the PFO section. It can be used to close secundum ASDs smaller than 17 mm. Similar to the GCSO, the Gore CARDIOFORM ASD Occluder consists of a nitinol wire frame covered with expanded PTFE (ePTFE). It has an LA and RA disk and an intra-disk region or waist between the disks that occupies the defect and prevents shunting of blood between the left and right atria. It is available in five sizes—27, 32, 37, 44, and 48 mm—and can treat a defect range of 8 to 35 mm. The delivery system consists of an 80-cm working length, an 10- to 14-Fr outer diameter delivery catheter, a control catheter, and a mandrel coupled to a handle.

Procedural Details

Atrial septal defect closure is usually performed in the cardiac catheterization laboratory with conscious sedation and ICE and fluoroscopic guidance (Figures 33.8 and 33.9) (Videos 33.3 and 33.4). For complex septal anatomy, such as multiple ASDs, TEE may be preferred. Advantages of ICE over TEE include no need for general anesthesia or additional cardiologists to perform the procedure, better views of the posteroinferior part of the interatrial septum, and shorter procedure times. Most operators use the AcuNav ICE catheter (Siemens Medical Solutions distributed by Biosense Webster), and other devices by Boston Scientific and GE Healthcare are commercially available. The initial steps are similar to those described for PFO closure. Aspirin 325 mg is usually administered before the procedure with a clopidogrel 600-mg loading dose at the end of the procedure. Femoral venous access is obtained in bilateral groins (or two sheaths in the same vein), one of which is for ICE. The authors prefer a 9-Fr, 35-cm sheath for the ICE catheter to easily traverse the iliac vein into the IVC, particularly for left femoral vein insertion. Heparin is administered to maintain an ACT greater than 250 seconds, and a dose of intravenous antibiotic is administered before device deployment.

A complete right heart catheterization is first performed to measure shunt fraction, PAPs, and pulmonary capillary wedge pressure. In patients older than 40 years, coronary angiography is also performed. The authors also perform pulmonary angiography with levo phase imaging to assess drainage of all four pulmonary veins into the left atrium. Some operators perform right upper pulmonary vein angiography in 35-degree LAO cranial projection, which provides an angiographic roadmap of the interatrial septum to facilitate closure.

The ICE catheter is advanced into the right atrium, and the interatrial septum is adequately interrogated for assessment of various rims, measuring defect size, and confirming pulmonary venous drainage. A rim is considered to be deficient if its length is smaller than 5 mm and absent if it is 1 mm or larger (Video 33.5). The rims should not be deficient (except anterior rim because many patients lack

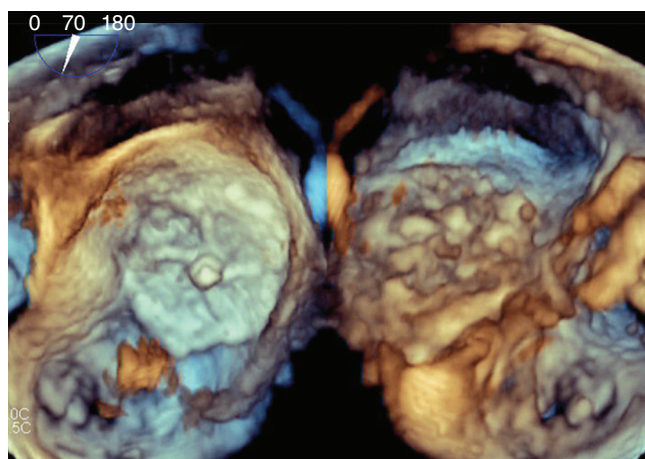


FIGURE 33.7 Three-dimensional transesophageal echocardiogram showing a well-seated 34-mm Amplatzer atrial septal defect Occluder.

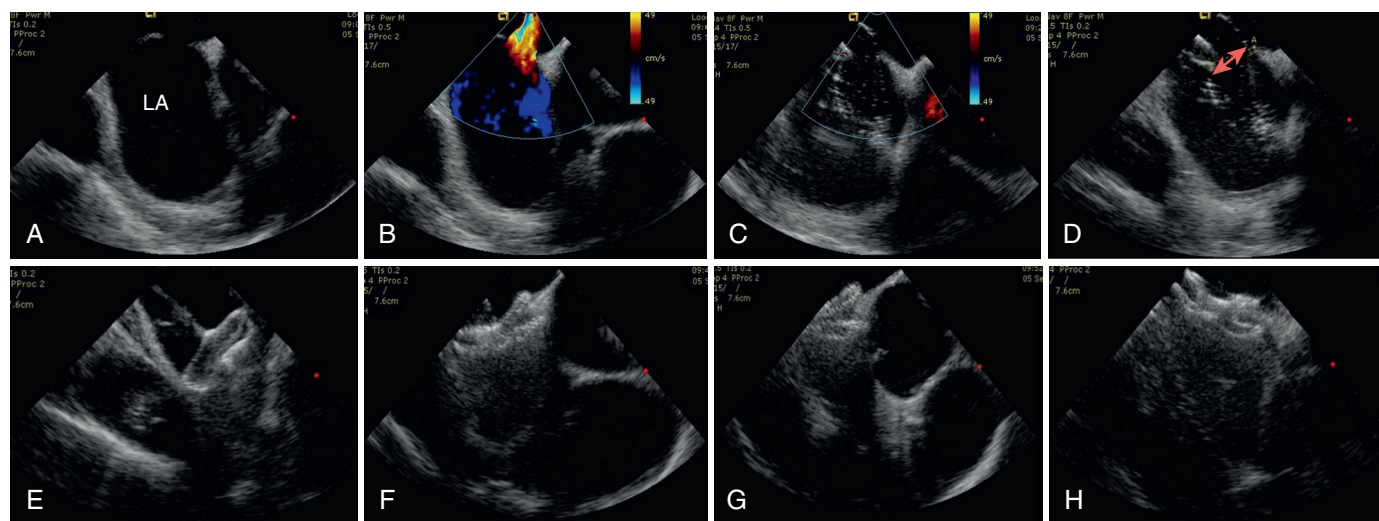


FIGURE 33.8 Intracardiac echocardiography (ICE) images during transcatheter secundum atrial septal defect (ASD) closure using the Amplatzer atrial septal Occluder device. **A** and **B**, Secundum ASD with two-dimensional and color Doppler by ICE. **C** and **D**, Balloon stop flow diameter, color Doppler, and two-dimensional ICE. **E**, Deployment of the left atrial disk. **F**, Deployment of the right atrial disk. **G**, Device splaying around the aorta. **H**, Final device position.

the anterior rim, and it is not a contraindication). The directions include a “warning” that a deficient aortic rim may incur increased risk of erosion, but data are insufficient as discussed later. After completion of hemodynamic assessment, angiography, and ICE assessment, a multipurpose catheter is advanced with a 0.035-inch J-tipped guidewire into the SVC. The catheter is moved in a caudal direction and then directed toward the interatrial septum and the ASD crossed with or without the 0.035-inch J-tipped guidewire using ICE and fluoroscopic guidance. The catheter and guidewire are placed in the left superior pulmonary vein, taking care to ensure that the wire tip is not in the LAA to avoid perforation. The 0.035-inch J-tipped guidewire is exchanged for a 0.035-inch, 1-cm Amplatz super-stiff wire, again with care taken to ensure that the tip is not in the appendage. Balloon sizing is the next step and is usually performed with an AGA sizing balloon or NuMED sizing balloon. Under fluoroscopic and ICE guidance, the balloon catheter is placed in the defect over the extra-stiff guidewire, and the balloon is gently inflated until no flow is visualized by color Doppler on ICE imaging (see [Figures 33.8](#) and [33.9](#)). It is very important to stop inflating when flow ceases (stop-flow diameter) to avoid oversizing the defect. This diameter is measured on ICE as well as fluoroscopy. For ASO, the device size should be equal to but no larger than 1 to 2 mm above the stop-flow diameter. The Gore CARDIOFORM ASD Occluder should be sized depending on the stop-flow diameter, with the largest defect being 35 mm.

The next steps depend on the device used. For the ASO device, the delivery sheath size ranges from 6 to 12 Fr depending on the device size chosen. The balloon-sizing catheter is removed, leaving the 0.035-inch wire in place. The delivery cable is passed through the loader, and the device is screwed to the tip of the delivery cable. The device and loader are immersed in sterile saline solution, and the device is pulled into the loader while flushing through the side arm. The delivery sheath is prepped, and the dilator is inserted into the sheath. The short sheath in the

femoral vein is removed, and the delivery sheath and dilator is then advanced over the 0.035-inch wire, which has been placed in the left upper pulmonary vein. The dilator is removed after it reaches the right atrium, and the sheath is de-aired. The sheath is then advanced over the wire into the left atrium, with care taken to avoid suction of air in the system. The guidewire is removed, and the sheath is flushed carefully. The loading device is then attached to the delivery sheath. Under fluoroscopic guidance, the device is advanced, carefully watching for any sign of air in the system. When the device is at the tip of the delivery sheath in the left atrium under fluoroscopic and echocardiography guidance the LA disk is deployed by retracting the sheath over the delivery cable. The device is gently pulled against the interatrial septum and with tension on the delivery cable; the sheath is retracted further to deploy the RA disk. After deployment, the position is checked by ICE, and if needed, a gentle “to-and-fro” motion (Minnesota wiggle) can be performed with the delivery cable to assure stable positioning. ICE assessment should include Doppler flow, which may still demonstrate flow through the waist (but should not be present around the disk), and evaluation for obstruction of adjacent structures, including atrioventricular valves. If the positioning is unsatisfactory or there is impingement of adjacent structures, the device is retracted back into the delivery sheath and redeployed or replaced with a new device as appropriate. Device positioning can also be confirmed by angiography in LAO cranial projection, which allows separation of the LA and RA disks. In cases in which the device impinges or indents on the aortic root, there may be higher risk of erosion. After satisfactory positioning is confirmed, the device is released by attaching the plastic vise to the delivery cable and rotating it counterclockwise.

Deployment of the Gore CARDIOFORM ASD Occluder begins with deployment of the LA disk by pushing the slider to the left until it stops. The slider is then pushed up and to the left, leading to a funnel-shaped formation of the Occluder with a circular left disk. The handle is then

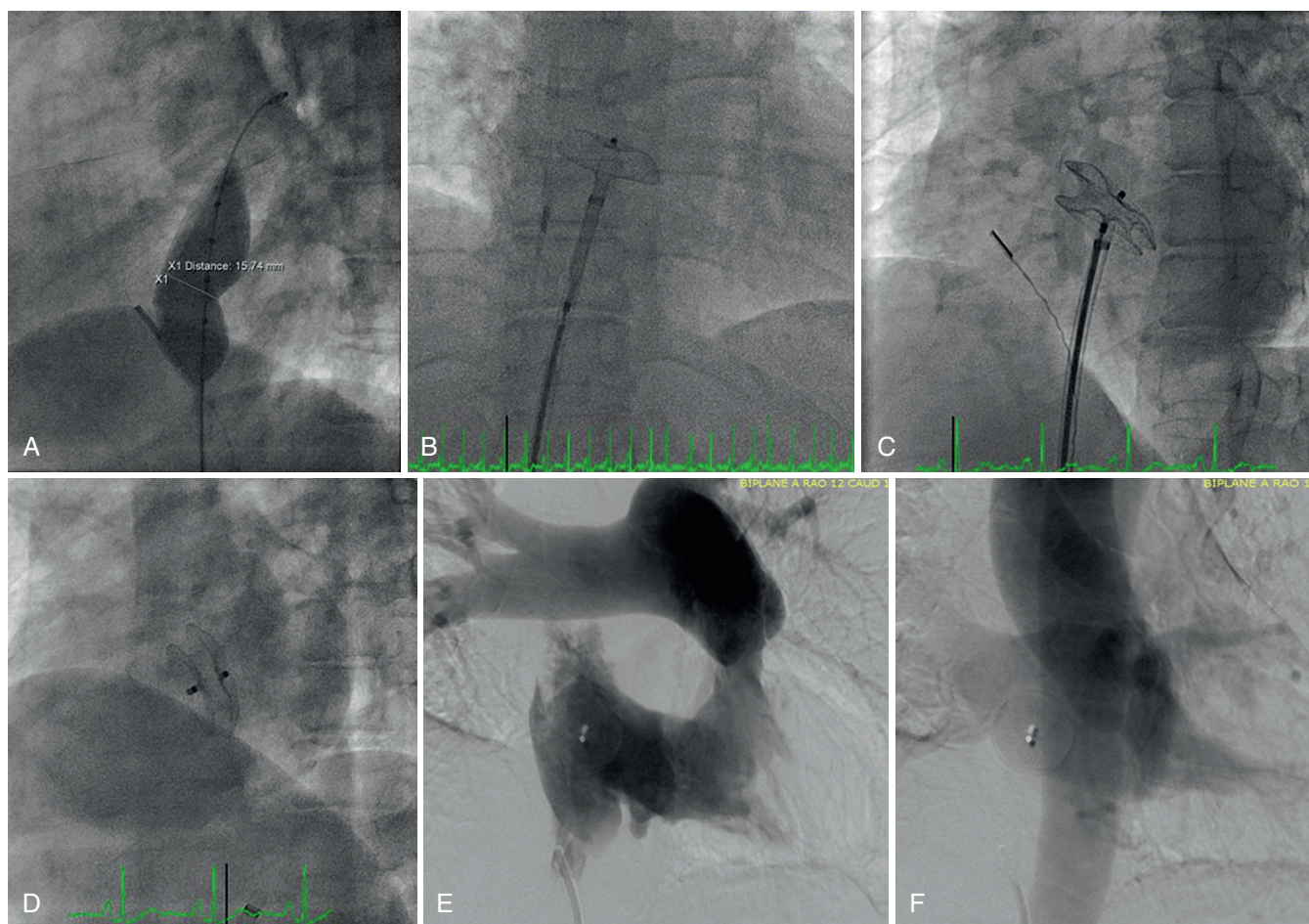


FIGURE 33.9 Fluoroscopic images during transcatheter secundum atrial septal defect (ASD) closure using Amplatzer atrial septal Occluder device. **A**, Balloon sizing. **B**, Deployment of the left atrial disk. **C**, Deployment of the right atrial disk. **D**, Final device position. **E** and **F**, Right atrial angiogram with levo phase imaging showing the well-seated device.

pulled to bring the LA disk on to the surface of the LA septum. The RA disk is then deployed by pushing the slider to the left until it stops and then down. The planar appearance of both the LA and RA disks and apposition to the septum are then confirmed. When the position and defect closure are acceptable, the device is locked, the retrieval cord lock is pulled up and disengaged from the slider, and then the retrieval cord lock is gently pulled until the retrieval cord is completely removed from the handle. The Occluder is thus released from the delivery system, which can then be removed.

Postprocedure Care

After device deployment, sheaths are removed, and hemostasis is achieved. Two doses of antibiotics are given 12 hours apart. Patients are monitored with telemetry overnight, and chest radiography and TTE with bubble study are performed the next morning to confirm accurate positioning. The patient is typically discharged on dual antiplatelet therapy (DAPT) with aspirin 81 mg/day and clopidogrel 75 mg/day for 6 months, after which aspirin 81 mg/day is continued. The RV size and device are reassessed at 6 months with TTE. Endocarditis prophylaxis is advised for 6 months.

Large Atrial Septal Defect with Deficient Rims

Atrial septal defects larger than 25 mm are most often associated with rim deficiency. The Gore CARDIOFORM ASD Occluder has been approved in 2019 for the treatment of large ASDs (≤ 35 mm) including ASDs with deficient retroaortic rims.⁵⁷ In cases of large ASDs with deficient superior, anterosuperior, or posteroinferior rims, the LA disk can prolapse through the defect during regular deployment. Techniques for closing large ASDs with deficient rims include sheath modifications or using special sheaths. The Hausdorf sheath (Cook Medical) is a double-curve sheath with an angled tip that keeps the disk parallel to the septum and away from the aortic rim. A modification of the Mullins sheath has been described for large ASDs with deficient anterior or posteroinferior rims, in which the distal curved portion of the sheath is cut off, resulting in a straight sidehole (SSH) delivery sheath.⁵⁸ The sharp end of the cut sheath is then trimmed to reduce the risk of perforation. The SSH technique allows the device to exit the tip of the delivery sheath at an angle parallel to the septum. Other techniques for large ASDs with deficient posterior rims include using a right Judkins catheter technique or a steerable curved guiding catheter such as the Agilis catheter (St. Jude Medical). The balloon-assisted technique consists of using a balloon as a buttress to

prevent prolapse of the LA disk through the ASD during deployment.⁵⁹

Multiple or Fenestrated Defects

Multiple defects are present in 10% of cases. They can often be treated with a single device. A second device is usually required if the distance between the primary and secondary defect is 7 mm or more. Other methods for closure with a single device include using a nonself-centering device such as the GCSO device or Amplatzer cribriform device.

Iatrogenic Atrial Septal Defects After Transcatheter Mitral Interventions

Mitral transcatheter edge-to-edge repair (TEER) and transfemoral transcatheter mitral valve replacement (TMVR) require transeptal access to the left atrium, and persistent iatrogenic ASD (iASD) has been reported in 25% to 50% of patients.⁶⁰ In the absence of large-scale randomized trial data, iASD closure has typically been performed after TEER or transfemoral TMVR in presence of right-to-left or bidirectional shunting, severe RV dysfunction, pulmonary hypertension, large iASD, or large shunt fraction. We typically perform closure under these situations with a 27-mm Gore CARDIOFORM ASD Occluder without balloon sizing. Recently, a small, randomized trial, MITHRAS (Closure of iatrogenic ASD following transcatheter mitral valve repair), was performed. In this trial, 80 patients with iASD and relevant left-to-right shunting (Qp/Qs ratio ≥ 1.3) 30 days after TEER were randomized to iASD closure or conservative therapy, and 235 patients without an iASD served as a comparative cohort. At 12-month follow-up after TEER, there was no significant difference in the combined endpoint of death or heart failure hospitalization between the two groups. Compared with patients without an iASD, the patients who underwent iASD closure had higher rates of heart failure hospitalization. This suggests that patients with an iASD are at higher risk for heart failure hospitalization independent of iASD management and should be followed closely.

Complications

The vast majority of complications with transcatheter ASD closure are minor. The ASO pivotal study, which enrolled 442 patients in the device group and 152 patients in the surgical group, had a major adverse cardiovascular event (MACE) rate of 1.6% in the device group compared with 5.2% in the surgical group.⁶¹ Similarly, in the Helex pivotal study, enrolling 119 patients in the device group and 128 patients in the surgical group, the MACE rate was lower in the device group compared with surgical group (5.9% vs 10.9%).⁶² Cardiac erosions are the most feared and life-threatening complications of ASD closure using the ASO device.⁶³ There have been less than a handful cases of erosions described with the Helex device and no cases of erosions with the new CARDIOFORM ASD Occluder.^{53,57} The erosion rate has been reported to be 0.1% to 0.3% (1–3 per 1000 implants) with the ASO device.^{63,64} Erosion

most commonly occurs in the roof of the atria or the aorta. Large device size and lack of anterior or superior rims have been proposed as risk factors associated with erosion.^{63,64} Lack of wiggle room in case of a large device with deficient rim can lead to constant impact on the atrial or aortic tissue from the edge of the device. A high-risk ASD is a large defect in the superior portion of the septum in close proximity to the aorta with absent or negligible aortic rim. Based on their findings, the AGA expert panel made recommendations regarding erosions, which include avoiding overstretching while balloon sizing, using stop-flow technique for sizing, gentle to-and-fro motion while assessing stability, and closer follow-up of those with large ASO (>1.5 times native ASD size) and those with deformation of the ASO device at the aortic root with significant splaying of the device edges by the aorta. These are based on an expert opinion and not verified conclusively in a prospective manner. There are still differences in opinion regarding risk of erosion. A survey of members of the Congenital Cardiovascular International Study Consortium showed that 71.7% believed that a device in which the disks approximated each other and touched or protruded into the aorta without splaying were at the highest risk of erosion.⁶⁵ The Circulatory System Devices Panel of the FDA met on May 24, 2012, to discuss current knowledge about the safety and effectiveness of the Amplatzer ASO device and Gore Helex ASD Occluder as transcatheter ASD Occluder devices used for the closure of secundum ASD. Between 2002 and 2017, 125 erosions were reported to St. Jude Medical with subsequent 9 deaths.⁶⁶ Most of the patients occurred within the first year, with a median of 14 days after the procedure. Risk factors included rim deficiency, device larger than ASD by more than 5 mm, and weight-to-device size ratio. In this perspective, it is reasonable to perform more frequent follow-up in the first year after closure because events frequently occurred within 12 months and to thoroughly discuss the risks and benefits with patients.

Device malposition or embolization can potentially occur with any ASD closure. Various causes include large, eccentric defect, inadequate rims, improper sizing, and operator-related technical issues. Embolization is the most frequent complication reported at a rate of 0.5% to 3%.⁶⁷ An analysis of the device embolizations reported to the FDA's MAUDE (Manufacturer and User Facility Device Experience) database showed that in 77% of cases, the device was retrieved using transcatheter approach, and in 17% of cases, surgical retrieval was needed.⁶⁸ There were two deaths related to device embolization. Most embolizations occur at the time of deployment or within 24 hours of the procedure. The operator must be familiar with transcatheter retrieval techniques using a gooseneck snare or biopptome. The most common site of embolization is the left atrium followed by the right atrium, pulmonary artery, right ventricle, left ventricle, and aorta.⁶⁷ If the device is stuck in the ventricle and entangled within the atrioventricular valve apparatus, the patient should be referred for surgical removal. Device embolization appears to be more frequent with the Helex device than the ASO device.

Other complications include wire frame fracture in the case of Gore Occluder devices, thrombus formation on the

device, new-onset atrial arrhythmias, and impingement of adjacent structures, including the atrioventricular valves. Wire fractures have been reported in up to 35% of patients undergoing closure with the Gore Occluder device, but no serious adverse events or reinterventions were reported thus far.⁵⁷

In the New GORE CARDIOFORM ASD occluder for transcatheter closure of atrial septal defect (ASSURED) clinical study that evaluated the safety and efficacy of the Gore CARDIOFORM ASD Occluder, 125 patients underwent the procedure with 96% and 88% technical and closure success rates at the conclusion of the procedure, respectively.⁵⁷ The device was implanted in 71 patients with deficient retroaortic rim. Atrial arrhythmias occurred in 6.4% of patients. Two patients (1.6%) had device embolizations. This study led to the FDA approval of the device.

Clinical Trial Data

Results are excellent with both Amplatzer and CARDIOFORM ASD Occluder devices with successful closure rates greater than 95% with both devices.^{57,62,69-71} Safety outcomes and complications have been discussed previously. Overall, the risk of complications is lower with the transcatheter closure approach than with surgical approach.^{61,72}

LEFT ATRIAL APPENDAGE CLOSURE

Introduction

Atrial fibrillation is the most common cardiac arrhythmia, affecting 7 million patients in the United States.⁷³ The lifetime risk of developing AF is one in four in men and women older than 40 years of age. Stroke, the most feared and serious complications of AF, is the third leading cause of death in the United States and the leading cause of disability. Patients with AF have a fivefold increased risk of stroke compared with the general population. The risk of stroke increases with age, 1.5% at 50 to 59 years, and nearly greater than 20% at 80 to 89 years have AF.⁷⁴ Strokes related to AF have been associated with higher morbidity and mortality compared with non-AF-related strokes.

Medical Therapy for Stroke Prevention in Atrial Fibrillation

A number of risk models have been developed to stratify the risk of stroke in patients with AF. For example, the most widely used CHADS₂ score consists of 1 point each for age older than 75 years, history of congestive heart failure, hypertension, and diabetes and 2 points for a prior embolic event.⁷⁵ The score ranges from 0 to 6, and the risk of stroke increases in an incremental fashion with increasing score (0.5% per year with score 0 to almost 7% per year with score 6 without warfarin).⁷⁶ CHADS₂-VASc score was further developed and demonstrated more accurate assessment of the thromboembolic risk. It incorporates the same variables as the CHADS₂ in addition to sex (female, 1 point) and vascular disease history (1 point) and minor changes in scoring age (age older than 75 years, 2 points; age 65–75 years, 1 point). The only medical option until recently for stroke prevention in patients with AF has been

anticoagulation with warfarin, which reduces the risk of stroke by 60% compared with placebo and by 30% to 40% compared with aspirin alone.⁷⁷ Of note, the risk of both intracranial and extracranial hemorrhage was higher with warfarin than with aspirin. Warfarin has also been shown to be superior in stroke prevention compared with DAPT with aspirin and clopidogrel.⁷⁸ Despite its efficacy, warfarin has several drawbacks. It has a narrow therapeutic range and requires frequent blood tests for monitoring. A significant risk of major bleeding of more than 10% per year is associated with warfarin use.⁷⁹ Additionally, the efficacy of anticoagulation is variable because of interactions with foods and other medications, and despite frequent monitoring and dosage adjustments, fewer than 50% of patients treated with warfarin have international normalized ratios (INRs) in the therapeutic range of 2.0 to 3.0. In addition, 40% of patients with AF have contraindications to warfarin.⁸⁰

Newer anticoagulants have emerged in the past few years. The oral direct thrombin inhibitor dabigatran was evaluated in the randomized evaluation of long-term anticoagulation therapy (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY] trial).⁸¹ In this study, 18,113 patients with AF and increased risk of stroke (mean CHADS₂ score, 2) were randomized to treatment with warfarin or dabigatran (110 or 150 mg twice daily) in a noninferiority design with primary endpoint of stroke or systemic embolism. The 110-mg dose of dabigatran proved noninferior to warfarin with respect to the primary endpoint with less major bleeding, whereas the 150-mg dose was associated with lower rate of the primary endpoint with similar major bleeding. A recent analysis from the RE-LY trial suggested that in patients 75 years of age or older, the risk of intracranial bleeding is lower, but the risk of extracranial bleeding is similar or higher with both doses of dabigatran compared with warfarin.⁸² Similarly, other newer agents such as apixaban and rivaroxaban have been studied for stroke prevention in patients with nonvalvular AF; however, these agents also carry the risk of bleeding as well as higher cost.^{83,84}

Left Atrial Appendage Anatomy

The LAA is an important cardiac structure located anterolaterally in the atrioventricular groove between the left ventricle and the left upper pulmonary vein. It originates from primordial atrial tissue and consists of trabeculated pectinate muscles, mostly in the mid and distal segments. There is wide variability in the shape, number of lobes, and volume of the LAA. An autopsy study of 500 hearts showed that 54% of LAA had two lobes, and 23% had three lobes unrelated to age or gender.⁸⁵ There is usually an elliptical ostial segment that is free of trabeculations. In sinus rhythm, the LAA has contractile function with an emptying velocity that can be distinctly recorded by TEE. In AF, there is stasis of blood in the LAA as a result of decreased contractility in conjunction with LA enlargement, leading to formation of thrombus. The LAA is the source of thrombus in the vast majority of patients (>90%) with nonvalvular AF and thromboembolic events as demonstrated by echocardiography.⁸⁶ Because of the several issues outlined earlier with anticoagulant therapy, surgical and recently percutaneous exclusion of the LAA has been developed.

Surgical Left Atrial Appendage Exclusion

Surgical LAA exclusion has been performed concomitantly in patients with AF undergoing heart surgery, such as aortic or mitral valve surgery, along with the maze procedure. There are several surgical techniques for LAA consisting of either excision or exclusion of the LAA. Excision is performed by removal of the LAA, either by scissors or a stapling device.⁸⁷ Exclusion of the LAA is performed by closing the orifice of the LAA surgically with a suture or by stapling. A high rate of late LAA patency after surgical techniques has been reported.⁸⁸ In one study using TEE after surgery, the rate of successful LAA closure was found to be only 40% with greater rate of successful closure with excision (73%) than suture exclusion (23%).⁸⁹ Additionally, concerns remain for increased postoperative bleeding after surgical LAA exclusion or excision. The benefit of surgical occlusion of the LAA was recently confirmed by the Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke (LAAOS) III trial, in which patients were randomized to either the occlusion group (2379 patients) or the no-occlusion group (2391 patients).⁹⁰ There were decreases in stroke and systemic embolism in the occlusion group at 3.8 years of follow-up (HR, 0.67; 95% CI, 0.53–0.85; $P = .001$). An important caveat is that 76.8% of patients remained on anticoagulation at 3 years of follow-up.

Transcatheter Left Atrial Appendage Closure

Several devices have been developed for transcatheter LAA closure. The ACC/AHA guidelines have given LAA closure a Class IIb recommendation for stroke prevention in patients with nonvalvular AF who have a contraindication to long-term anticoagulation. This was based on three RCTs (PROTECT AF [WATCHMAN Left Atrial Appendage System for Embolic PROTECTION in Patients With Atrial Fibrillation], PREVAIL [Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy], and PRAGUE-17 [Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in High-Risk Atrial Fibrillation Patients]) and other observational and registry studies. LAA closure devices have also been used in patients who refuse anticoagulation or have recurrent cardioembolic events despite use of oral anticoagulants. The devices and the data available are summarized later.

Imaging for Left Atrial Appendage Closure

Transcatheter LAA closure is performed under fluoroscopic and TEE guidance. Although these modalities provide “real-time” imaging, they are limited by the two dimensional (2D) nature of data obtained. TEE is also very useful in ruling out LAA thrombus. 3D TEE can help determine the shape and dimensions of the LAA ostium. Multidetector CT (MDCT) acquires a 3D dataset, which allows reconstruction and provides more precise procedural planning as compared with 2D planning for structural interventions such as transcatheter aortic valve replacement (TAVR). A recent study outlined the use of MDCT for preprocedural planning for LAA closure.⁹¹ In this study, poor correlation was found between TEE measurements and those provided by MDCT. A strategy for assessing the LAA anatomy for percutaneous

LAA closure was outlined and various measurements defined such as distance from the fossa ovalis to the LAA ostium in three planes, distance from the LAA to the surrounding structures, assessment of sphericity of the LAA ostium, angulation of the appendage with reference to the ostial plane, presence of trabeculations and pectinate muscle, and methods to predict optimal fluoroscopic views during percutaneous LAA closure procedure. It is possible that better assessment of 3D anatomy by MDCT will help in optimal sizing of the LAA closure device and reduce the chances of complications by minimizing manipulation of wires and devices in the left atrium. Although clinical trials used TEE, currently there is a growing trend toward using CT, both before and after LAA closure for device sizing and assessing for peridevice leaks, respectively.

Watchman and Watchman FLX Devices

The Watchman device (Boston Scientific) is a self-expanding parachute-shaped nitinol frame with fixation barbs and polyester membrane covering the frame on the LA side. The device is available in five sizes with diameters ranging from 21 to 33 mm and thus is suitable for a maximal LAA ostial sizes between 17 and 31 mm. The Watchman device is the most studied percutaneous LAA closure device with more than 200,000 implants worldwide. This device has been evaluated in the PROTECT AF trial, the continued access protocol (CAP) registry, and the PREVAIL trial. The Watchman device gained CE Mark in 2005 and US FDA approval in 2015.

Watchman FLX is the next generation of the Watchman device that is 10% to 20% shorter, is available in five sizes with diameters ranging from 20 to 35 mm, and is suitable for maximal LAA ostial sizes between 15 and 32 mm. The device has more struts and anchors and gained CE Mark in 2015 and FDA approval in the United States in 2020.

Procedure

The procedure is typically performed under TEE or ICE and fluoroscopic guidance (Figure 33.10 and Video 33.6). After transseptal puncture is performed in standard fashion (mid or inferior posterior and not high), a pigtail catheter is advanced into the LAA to perform LAA angiography. Using angiography and echocardiography (intraprocedural ICE or TEE) and preprocedural CT as described earlier, the appropriate size of the device to be used is determined. The LAA ostium is often ellipsoid,⁹¹ and the device is generally sized 10% to 20% larger than the LAA ostium. The device is advanced via the delivery system through a 12-Fr transseptal sheath (outer diameter, 14 Fr). The device is positioned, and stability is verified by fluoroscopy and TEE before release.

Data for the Watchman Device

The PROTECT AF study was the first prospective RCT that examined the safety and efficacy of percutaneous LAA closure compared with anticoagulant therapy with warfarin (noninferiority study) in patients with nonvalvular AF.⁹² Patients aged 18 years or older with paroxysmal, persistent, or permanent AF and CHADS2 scores of 1 greater were included. Patients with contraindications to warfarin, LAA thrombus, PFO with ASA and right-to-left shunt, mobile

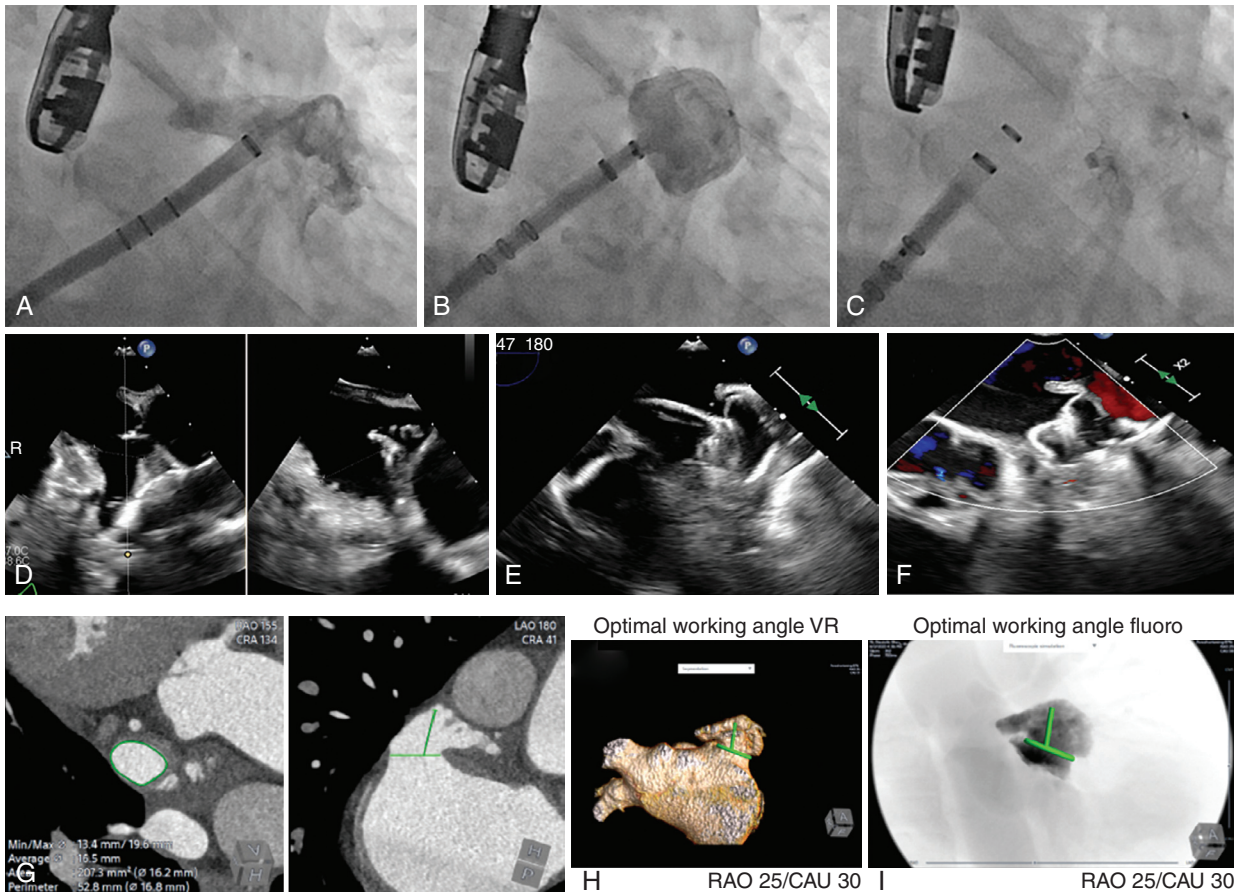


FIGURE 33.10 Fluoroscopic, transesophageal echocardiography (TEE), and cardiac computed tomography (CT) images before and during transcatheter left atrial appendage (LAA) closure using a Watchman FLX device. **A**, LAA angiogram with pigtail. **B**, LAA angiogram with the Watchman FLX device in position in LAA. **C**, Device deployment. **D**, LAA measurements using TEE for device sizing. **E** and **F**, Two-dimensional and color Doppler TEE image showing the Watchman FLX device in LAA. **G** and **H**, LAA measurements using cardiac CT for procedural planning and device sizing. CAU, right anterior oblique; VR, virtual reality.

aortic atheroma, and symptomatic carotid artery disease were excluded. A total of 707 patients were randomized in a 2:1 ratio to percutaneous LAA closure and subsequent discontinuation of warfarin 45 days later (intervention group, $n = 463$) followed by DAPT for 6 months and then aspirin monotherapy or to warfarin therapy with target INR between 2.0 and 3.0 (control group, $n = 244$). The implantation success rate was 88%. At 1065 patient-years of follow-up (mean follow-up period per patient, 18 months), the primary efficacy event rates (composite of stroke, cardiovascular death, and systemic embolism) were 3.0 per 100 patient-years (95% CI, 1.9–4.5) in the intervention group and 4.9 per 100 patient-years (95% CI, 2.8–7.1) in the control group (RR, 0.62; 95% CI, 0.35–1.25) with a probability of noninferiority of the intervention greater than 99.9%. The primary composite safety endpoint (bleeding or procedure-related complications such as serious pericardial effusion, device embolization, or procedure-related stroke) occurred more frequently in the intervention group than the control group (7.4 per 100 patient-years; 95% CI, 5.5–9.7, vs 4.4 per 100 patient-years, 95% CI, 2.5–6.7; RR, 1.69, 1.01–3.19). The most frequent complication in the intervention group was serious pericardial effusion (defined as the need for percutaneous or surgical drainage), which occurred in 22 (4.8%) of patients, of whom 15 patients

were treated with pericardiocentesis and 7 underwent surgical intervention. Device embolization occurred in 3 patients (0.6%), and procedure-related stroke occurred in 5 patients (1.1%). There was a learning curve as reflected in the decline in rate of serious pericardial effusion with increasing operator experience at each site. Because patients who were not candidates for warfarin therapy were excluded, PROTECT AF did not address the role of percutaneous LAA closure in patients with contraindications to warfarin therapy. Subsequently, the patients were followed for an extended period of 3.8 ± 1.7 years, and it was noted that the device group was not only noninferior but also superior to the medical therapy group in the primary efficacy outcomes. Cardiovascular death and all-cause mortality was lower in the device group.⁹³

The PREVAIL randomized trial also evaluated the safety and efficacy of the Watchman closure device compared with chronic warfarin use.⁹⁴ A total of 407 patients (with CHADS2 score ≥ 2) were randomized in a 2:1 ratio and followed for a mean of 12 ± 8 months. The implantation success rate was 95.1%. The study was unable to meet the noninferiority criteria of the first coprimary efficacy endpoint (composite of stroke, cardiovascular or unexplained death, and systemic embolism) (6.4% in the device group vs 6.3% in the medical therapy group; RR, 1.07; 95% CI,

0.57–1.89. The second coprimary efficacy endpoint (stroke or systemic embolism >7 days) met the noninferiority boundary with a rate of 2.53% in the device group versus 2% in the medical therapy group. Mortality, ischemic stroke, and hemorrhagic stroke rates were 2.6%, 2.3%, and 0.4%, respectively. Periprocedural complications (pericardial effusions, 1.9%; device embolizations, 0.6%) were numerically lower than those encountered in the PROTECT AF trial. These landmark studies led to the FDA approval of the Watchman device for stroke prevention in AF in 2015.

The CAP registry evaluated 460 patients undergoing LAA closure with the Watchman device after the PROTECT AF study and demonstrated significant decline in procedure-related complications with greater operator experience.⁹⁵ The registry showed a significantly lower rate of serious pericardial effusion (2.2%, a 58% RR reduction from PROTECT AF), procedure-related stroke (0%), and overall procedure- or device-related safety adverse events (3.7%).⁹⁴

The ASAP (Aspirin Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology) study was the first study to assess the safety and efficacy of LAA closure in patients with nonvalvular AF who were ineligible for warfarin therapy.⁹⁶ In this multicenter, prospective, nonrandomized study, 150 patients with AF and CHADS₂ scores greater than 1 who were ineligible for warfarin because of history of bleeding or high risk for bleeding underwent LAA closure with the Watchman device. The patients received DAPT for 6 months followed by aspirin indefinitely. The implant success rate was 94.7%. Over a mean follow-up period of 14.4 ± 8.6 months, the rates of all-cause stroke or systemic embolism was 2.3 per 100 patient-years, the rate of ischemic stroke was 1.7 per 100 patient-years, and the rate of hemorrhagic stroke was 0.6 per 100 patient-years. Based on the mean CHADS₂ score of 2.8, the annual ischemic stroke rate was expected to be 7.3% with aspirin alone. The observed rate of 1.7% represents a 77% risk reduction. Pericardial effusion with tamponade requiring percutaneous drainage occurred in 1.3% of patients, and device embolization occurred in 1.3% of patients. The ASAP study showed that LAA closure with the Watchman device can be safely performed without warfarin transition and can be used in patients with AF at high risk for bleeding who are unable to tolerate oral anticoagulation.

The EWOLUTION (Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial) trial was a prospective nonrandomized cohort study that enrolled 1025 patients from 47 centers in 13 countries.⁹⁷ The baseline CHADS₂-Vasc₂ score was 4.5 ± 1.6 . Only 5 patients were unsuitable for device implantation, and the implant success rate was 98.5%. Antithrombotic therapy consisted of DAPT (60%), Single antiplatelet therapy (SAPT) (7%), vitamin K antagonist (16%), direct oral anticoagulant (DOAC) (11%), and none in 6. The rate of ischemic stroke was 1.1%, significantly lower than the expected rate based on CHADS₂-Vasc₂ of 7.2%. Device embolization and pericardial effusions occurred in 0.2% and 0.3% of the cases, respectively.

Data from the National Cardiovascular Data Registry Left Atrial Appendage Occlusion (NCDR LAAO) Registry

was published in 2020, including 38,158 procedures performed in 495 hospitals.⁹⁸ The mean CHADS₂-Vasc₂ was 4.6 ± 1.5 . The implantation success rate was 92.8%, and the mortality was low at 0.19%. The most common complications included pericardial effusion (1.4%) and major bleeding (1.25%).

The PINACLE-FLX (Primary Outcome Evaluation of a Next-Generation Left Atrial Appendage Closure Device: Results From the PINNACLE FLX trial) trial was a prospective single-arm nonrandomized study that evaluated the efficacy and safety of the new generation of Watchman (Watchman FLX).⁹⁹ The procedure was performed in 400 patients with a mean CHADS₂-Vasc₂ score of 4.2 ± 1.5 . The implant success rate was 98.8% and was associated with a low rate of complications (0.5%). The device-related thrombosis (DRT) rate was 1.8%. The authors concluded that the newer generation device is associated with a low incidence of adverse events.

Real-world data from the SURPASS registry were recently presented and included 45-day follow-up with Watchman FLX device in more than 16,000 patients (Cardiovascular Research Technologies, CRT 2022 scientific sessions).¹⁰⁰ Implantation was successful in 97.6% of patients, the key safety endpoint—a composite of all-cause death, stroke, systemic embolism, or device- or procedure-related events requiring surgery or major endovascular intervention at 7 days after implantation occurred in 0.37% of patients compared with 0.5% in the PINNACLE FLX trial. At 45 days, rates of adverse events were 0.91% for death, 0.38% for stroke, 0.23% for DRT, 0.03% for device embolization, and pericardial effusion requiring surgical or percutaneous intervention in 0.32% at discharge and 0.5% at 45 days.

Peridevice Leak

Peridevice leak (PDL) is encountered in 32% of LAAO at 1-year follow-up.¹⁰¹ PDL is related to an incomplete seal of the LAA ostium by the device (Video 33.7). Previously, a PDL of 5 mm or less was considered benign, with no association with poor outcomes. More recent data have demonstrated that small PDLs 5 mm or less, diagnosed at 1-year follow-up, increase the risk of thromboembolism, predominantly nondisabling stroke, without affecting mortality rates at 5 years.¹⁰² The current management of PDL includes long-term oral anticoagulation or consideration of obliteration of the PDL using endovascular approaches (endovascular coils and plugs). Very large PDLs are a consideration for a second LAAO device insertion. PDL closure is successful in 90% of cases, and successful discontinuation of anticoagulation was described in 81% of patients.¹⁰³

Device-Related Thrombus

Device-related thrombus is encountered in 2% to 5% of patients (Video 33.8).^{95,96,104-106} DRT remains a challenge and is associated with a higher risk of death and ischemic events (stroke or systemic embolization) (HR, 2.37; 95% CI, 1.58–3.56; $P < .001$).¹⁰⁷ Patients with hypercoagulable disorders, pericardial effusion, renal insufficiency, deep implantation of device (depth >10 mm from the pulmonary

vein limbus), and nonparoxysmal AF are more prone to DRT.¹⁰⁷ A lack of endothelialization can also increase the risk of DRT. Therapeutic options for DRT are limited, and there is no clinical consensus on management of DRT because patients who undergo LAAO are at high risk for bleeding and are not good candidates for long-term anticoagulation. Short-term anticoagulation has been successfully used to resolve DRT, but some cases require a longer duration along with imaging surveillance.¹⁰⁸ The optimal surveillance duration and strategy remain uncertain.

Amplatzer Cardiac Plug

The Amplatzer cardiac plug (ACP) (Abbott) is a self-expandable device made from braided nitinol wires, consisting of a distal lobe and proximal disk connected by an articulating waist. There are eight sizes, ranging from 16 to 30 mm, corresponding to the lobe diameter. The lobe has a fixed length of 6.5 mm, and the disk diameter ranges from 20 to 36 mm. The lobe has up to six stabilizing hooks that help anchor the device in the LAA. It can be delivered via a 9-, 10-, or 13-Fr sheath depending on device size.

Data for Amplatzer Cardiac Plug Device

The initial European experience of LAA closure with ACP device in 143 patients showed a procedural success rate of 96% and major complication rate of 7%, including 3 patients with ischemic stroke, 2 patients with device embolization, and 5 patients with clinically significant pericardial effusions.¹⁰⁹ In a single-center 10-year experience consisting of ACP implantation in 120 patients with nonvalvular AF, the combined rate of death, stroke, and systemic embolization was 7% during follow-up and the periprocedural rate of complications, including pericardial effusion, device embolization, procedure-related stroke, and major bleeding, was 6.7%.¹¹⁰ The largest multicenter registry, published to date, included 1047 patients with a mean age of 75 years and CHADS2 scores of 2.8 ± 1.3 .¹¹¹ The procedural success rate was 97.3% with a low periprocedural

complication rate of 4.3%. Around 73% of the patients had contraindications to oral anticoagulants. Most of the patients (68.9%) received SAPT after the procedure and had lower bleeding rates compared with the rest of the cohort. The RRs reduction of systemic thromboembolism and major bleeding were 59% and 61%, respectively. DRT was seen in 4.4% during the follow-up period of 13 months.

Amulet

The Amulet device (Abbott), a self-expanding device consisting of a nitinol mesh with two polyester patches sewn on to a distal lobe and a proximal disk connected by a short waist, received CE Mark approval in Europe in 2013 and FDA approval in 2021. It has several differences compared with the ACP, including a larger disk diameter, longer lobe and waist length, more sizes available (≤ 34 mm), and a stiffer stabilizing wire system. The Amulet device also has a recessed end screw to reduce risk of thrombus formation, has more stabilizing wires, and is preloaded in the delivery system. Moreover, the device has a dual-seal mechanism (Figure 33.11). These modifications were made to improve implantation and sealing with the device (Video 33.9).

The Prospective Global Amulet Observational registry study was the largest to date and included 1088 patients with a mean age of 75 years and CHADS VASc scores of 4.2 ± 1.6 .¹¹² The implant success rate was 99%, and the mortality rate during follow-up was 8.4%. The nonprocedural major bleeding rate was high at 10.3% per year, and the rate of DRT was 1.7%.

Amulet versus Watchman

The Amulet or Watchman Device for Percutaneous Left Atrial Appendage Closure (SWISS-APERO) randomized clinical trial was the first study to randomize 221 patients with nonvalvular AF to Amulet device implantation (111 patients) or Watchman device implantation (110 patients, 85 of whom received Watchman FLX) at eight European centers.¹¹³ The primary endpoint was the composite of justified crossover to other LAA devices during the

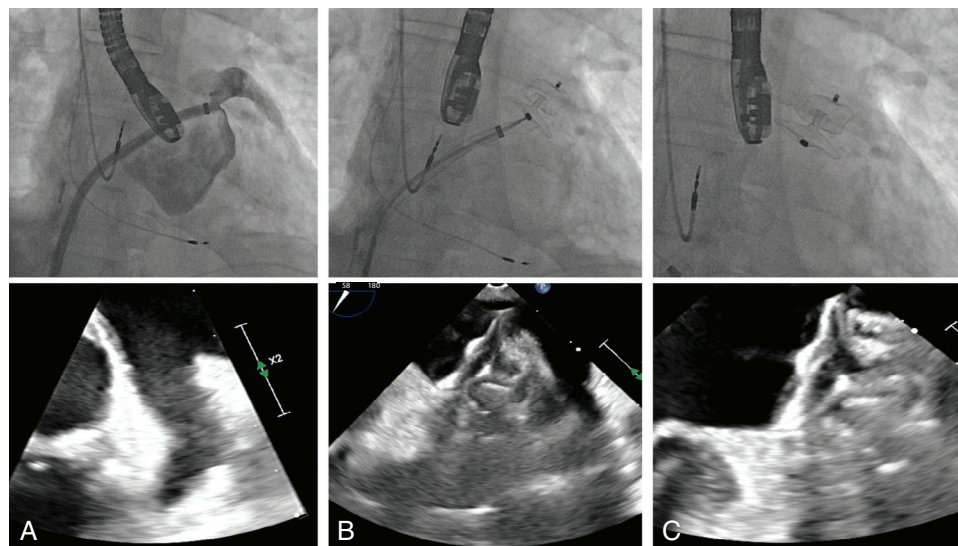


FIGURE 33.11 Fluoroscopic and transesophageal echocardiography (TEE) images during transcatheter left atrial appendage (LAA) closure using an Amulet device. **A**, LAA angiogram and visualization on TEE. **B**, Device deployment. **C**, Final device position.

procedure and residual patency at 45 days and did not significantly differ between the two groups. Only one patient crossed over in the Amulet group. At 45 days, intradevice leak was encountered more often in the Amulet group (44.8% vs 23%; $P = .001$), as opposed to peridevice leak, which was seen more frequently in the Watchman group (27.5% vs 13.7%). Only 1 patient developed DRT in the Amulet group and 3 patients in the Watchman group.

The Amulet-IDE (Amplatzer Amulet) was the largest randomized multicenter study comparing the Amulet Occluder device and the Watchman device for LAA closure.¹¹⁴ The study randomized 1878 patients with nonvalvular AF at high risk of stroke and bleeding to the implantation of an Amulet device versus a Watchman device. The primary endpoints included safety, effectiveness, and LAA seal at 45 days. Whereas around 76% of patients in the Amulet group were discharged on DAPT, 82% of patients in the Watchman group received a combination of warfarin and aspirin. At 12 months, there was no difference in the safety primary outcome between Amulet and Watchman (14.5 % vs 14.7%; $P < .001$). At 18 months, the Amulet device was as effective as the Watchman device in preventing ischemic stroke or systemic embolism (2.8% vs 2.8%, $P < .001$). The implantation success rate was slightly higher in the Amulet group (9 failed implantations vs 30 failed implantations in the Watchman group). At 45 days, the rate of LAA occlusion was higher in the Amulet group (98.9% vs 96.8 %; $P < .001$), with leaks being smaller in the same group. Finally, there was a slightly higher rate of hemorrhagic stroke in the Watchman group, which might have been as a result of the anticoagulation regimen after the procedure (warfarin with aspirin vs DAPT in the Amulet group).

PRAGUE-17 was a noninferiority randomized controlled study that evaluated patients with a high bleeding risk and a history of cardioembolic stroke to LAA closure (Amulet, 61%; Watchman, 36%; Watchman FLX, 3%) versus DOACs.¹¹⁵ The study included 402 patients (201 in each group) with CHA₂DS₂ VASc scores of 4.7 ± 1.5 , and most of the patients in the medical therapy arm were treated with apixaban (95.5%). At 19.9 months, the primary endpoint (composite of stroke, TIA, systemic embolism, cardiovascular death, major or nonmajor clinically relevant bleeding, or procedure- or device-related complications) was noninferior in the intervention group compared with the anticoagulation group (HR, 1.00; 95% CI, 0.40–2.51). At 4 years of follow-up, LAA closure remained noninferior to DOACs in the composite outcome of cardioembolic stroke, cardiovascular death, procedure-related complications, and clinically relevant bleeding (HR, 0.81; 95% CI, 0.56–1.18; $P = .27$; $P = .006$).¹¹⁶

LARIAT Device

The LARIAT (Sentre HEART) is a percutaneous epicardial suture device for LAA exclusion. It consists of 0.025-inch and 0.035-inch magnet-tipped guidewires (FindrWire), a 15-mm compliant occlusion balloon catheter (EndoCATH), and a 12-Fr suture delivery device (Lariat). Preprocedural CT angiography is very useful in assessing the size, shape, and orientation of the LAA and in guidance of the pericardial access. Because the width of the Lariat is 40 mm, LAA

width greater than 40 mm is a contraindication for this technique. Other contraindications include very superiorly oriented LAA or LAAs with the apex directed behind the pulmonary trunk.

In a single-center prospective series consisting of 89 patients with nonvalvular AF and contraindications to warfarin therapy undergoing LAA ligation using the Lariat device, 85 patients (96%) had successful procedure with 81 patients having complete closure (defined as <1 mm jet by color-flow Doppler) immediately.¹¹⁷ Complete closure of the LAA was observed in 98% of patients undergoing 1-year follow-up. There were three access-related complications—two during pericardial access and one related to transseptal catheterization. Severe pericarditis occurred in two patients after the procedure. Other smaller series have demonstrated similar feasibility and low incidences of complications.^{118,119} A multicenter registry included 712 patients and showed a successful implantation rate of 95% but a high number of cardiac perforations (24 patients). In July 2015, the FDA issued a safety alert that affected the use of the device in a large number of medical centers. Subsequently, the procedure was made safer with the use of micropuncture needles instead large-bore pericardiocentesis access, as well as the use of carbon dioxide to expand the pericardial space.^{120,121}

Most important, the FDA issued a safety alert (regarding cardiac perforation, complete LAA detachment) in July 2015, which negatively affected the use of the Lariat device in the United States.

Other Left Atrial Appendage Closure Devices

Coherex

The Coherex WaveCrest Left Atrial Appendage Occluder (Coherex Medical) consists of a nitinol frame supporting a polyurethane foam and ePTFE membrane. There are independent and retractable anchors to stabilize the device and a distal injection port to assess device stability during implantation. The device is positioned first, and the anchors are rolled out subsequently. There are three sizes (22, 27, and 32 mm) to accommodate LAA sizes between 18 and 30 mm.

Other devices are currently being studied and include endocardial devices, such as the WaveCrest (Biosense Webster), Occlutech (Occlutech International), LAMBRE (Lifetech Scientific), and Ultraseal (Cardia), and epicardial devices such as Sierra (Aegis Medical Innovations).

VENTRICULAR SEPTAL DEFECT

Introduction

Ventricular septal defect is the most common congenital heart defect presenting at birth with a prevalence of almost 4 per 1000 live births.¹²² The frequency varies with age at detection because many small defects present at birth may close spontaneously with time. VSD is often a part of complex congenital anomalies such as tetralogy of Fallot, transposition of the great vessels, aortic coarctation, and so on. These are usually diagnosed and treated during childhood. We focus on isolated VSD in this chapter.

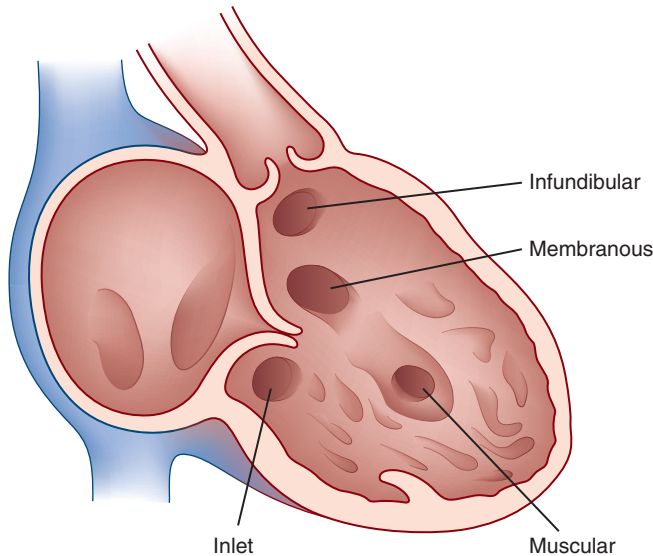


FIGURE 33.12 Location of various types of ventricular septal defects viewed from the right ventricular aspect.

Anatomy

Ventricular septal defects are classified based on their location in the interventricular septum (Figure 33.12).⁵⁴ VSDs in the outflow portion of the right ventricle are type 1 VSDs and are also referred to as subpulmonary, infundibular, supracristal, or doubly committed juxtaarterial VSDs. These account for about 6% of defects and rarely close spontaneously. Defects in the membranous septum, adjacent to the septal leaflet of the tricuspid valve, are referred to as type 2, or perimembranous, VSDs. These account for almost 80% of all VSDs and can be associated with adherence of the septal leaflet of the tricuspid valve to the defect, leading to formation of a pouch or “aneurysm” of the septum. Type 3, or inlet VSDs, occur in the inlet septum separating the mitral and tricuspid valves and area called atrioventricular septal defects. Type 4, or muscular VSDs (5%–20% of VSDs), can be located anywhere in the muscular septum and are surrounded by muscular rims. These can be multiple, and spontaneous closure is common. Acquired muscular VSDs are most often related to an acute myocardial infarction (MI) or trauma. Anterior infarctions are more likely to cause apical VSDs, and inferior or lateral infarctions are more likely to cause basal defects at the junction of the septum and the posterior wall.

Pathophysiology

Ventricular septal defect leads to shunting at the ventricular level. Factors affecting the hemodynamic impact of VSD include size of the defect, pressure in the right and left ventricles, and the relative resistances of the pulmonary and systemic vascular beds. Small defects that are less than 25% the size of the aortic annulus have small net left-to-right shunt and are sometimes referred to as restrictive defects. With larger or nonrestrictive defects, the shunt volume is determined primarily by the size of the defect and PVR. At birth, there may be minimal left-to-right shunting caused by high PVR. As the PVR decreases, left-to-right

shunting increases, and the defect becomes clinically apparent. In the absence of pulmonary hypertension or RV outflow obstruction, the direction of shunting is left to right with consequent LA and LV volume overload. In the presence of pulmonary hypertension or RV outflow obstruction, shunting may be right to left, depending on the pressure difference. Eisenmenger’s physiology results from chronic left-to-right shunting with structural changes in the pulmonary vasculature, resulting in irreversible pulmonary hypertension and reversal of shunt and consequent systemic desaturation and cyanosis. Secondary abnormalities related to VSD include prolapse of the right cusp of the aortic valve with resultant aortic regurgitation in case of infundibular VSD and tricuspid aneurysm formation secondary to adherent tricuspid valve leaflet into a perimembranous VSD. In cases of post-MI VSD, large left-to-right shunting occurs acutely, often leading to hemodynamic instability and circulatory collapse, depending on the size of the defect, the presence of RV infarction, and stunning of the right ventricle from volume overload.

Clinical Presentation

Adults with VSD usually have had a prior diagnosis or evaluation. VSD may present in several possible ways: patients with a small left-to-right shunt caused by a restrictive VSD may remain asymptomatic and present with a systolic murmur, patients with moderate-sized VSD may remain asymptomatic or develop symptoms of heart failure in childhood, and patients with large VSDs typically develop symptoms of heart failure during infancy. Other presentations include infective endocarditis; new diastolic murmur secondary to aortic regurgitation in cases of aortic valve prolapse with infundibular VSDs; and Eisenmenger syndrome with cyanosis, clubbing, and marked exercise intolerance in late childhood or adulthood.

Diagnosis

Clinical examination is characterized by a systolic murmur at the left lower sternal border. The intensity and duration of the murmur depend on the size of the VSD and RV pressure. Smaller defects are loudest. With low RV pressure, the murmur is usually holosystolic. Pulmonary hypertension and high RV pressure are usually associated with a RV heave, accentuated pulmonary component of second heart sound, and diminished or no murmur. The electrocardiogram can be normal in patients with small VSDs. In patients with large VSDs, there may be evidence of left-sided volume overload in the form of LV hypertroph or biventricular hypertrophy in those with associated pulmonary hypertension.

Echocardiography is the main imaging modality for diagnosis of VSD. TTE is very useful in delineating the location, size, and number of defects and in assessing the hemodynamic impact of the defect by estimating the RV systolic pressure; left and RV size and function; and associated abnormalities such as aortic regurgitation, tricuspid regurgitation and RV, or LV outflow obstruction. TEE may be necessary in patients with poor TTE windows. 3DE can be useful for quantifying shunts and for assessing defects

that are difficult to visualize by 2D echocardiography. MRI can be used to evaluate VSDs with associated complex congenital lesions and to calculate shunt fraction.

Cardiac catheterization is recommended in patients with VSD and pulmonary hypertension to accurately measure PVR, pulmonary reactivity, and degree of shunting.⁵⁴ Angiography can show the location of the defect but is usually not required because echocardiography delineates this well.

Management and Indications for Ventricular Septal Defect Closure

The treatment of patients with VSD depends on the size and type of defect; PAP and resistance; and associated acquired complications, including double-chambered right ventricle and aortic regurgitation. A small VSD in the absence of symptoms or evidence of LV volume overload does not require any intervention. Careful follow-up and monitoring are required in patients with VSD without signs of LV volume overload. Medical management is recommended in patients with large defects and irreversible pulmonary hypertension or Eisenmenger syndrome. Such patients should be cared for in specialized centers with expertise in managing a wide range of medical conditions that could arise in these cases. Vasodilator therapy can be an important adjunct and can provide functional improvement. In the current era, most adults presenting with unrepaired VSD likely have a small defect without LV volume overload or have residual shunt after previous operation. According to the ACC/AHA guidelines, the indications for VSD closure include the following:

- Class I: Qp/Qs ratio of 2 or more and clinical evidence of LV volume overload and history of infective endocarditis
- Class IIa: Closure of VSD is reasonable when net left-to-right shunting is present at a Qp/Qs ratio greater than 1.5 with pulmonary artery pressure less than two-thirds of systemic pressure and PVR less than two-thirds of systemic vascular resistance or Qp/Qs ratio greater than 1.5 in the presence of LV systolic or diastolic failure.
- Class III: VSD closure is not recommended in patients with severe irreversible pulmonary hypertension.

Primary surgical repair of VSD includes patch closure with a synthetic material (e.g., Dacron, PTFE) and concomitant repair of associated defects if present, such as resection of RV outflow obstruction in case of double-chambered right ventricle, aortic valve repair, or replacement in cases of aortic regurgitation. Intraoperative TEE is indicated to evaluate for additional defects and to assess the adequacy of repair. Observational data suggest that surgical closure decreases the risk of endocarditis by at least 50%, reduces pulmonary artery pressure, and improves long-term survival rates.¹²³⁻¹²⁵ Early mortality rates are low in the absence of elevated PVR, and late survival rates are excellent in the presence of normal ventricular function. In a series of 516 patients who underwent surgical VSD repair, the 25-year survival rate was 83%.¹²⁶ However, the long-term survival rate is significantly lower when repair is performed at an older age or in the presence of pulmonary hypertension.^{124,125} Despite a good

prognosis after surgical repair of uncomplicated VSDs, long-term sequelae can occur and include arrhythmias, residual VSD, endocarditis, tricuspid and aortic regurgitation, ventricular dysfunction, and pulmonary hypertension.

Over the past decade, transcatheter techniques for VSD closure have been developed. Indications for transcatheter VSD closure include muscular VSD, particularly when it is remote from the tricuspid valve and aorta and associated with evidence of LV volume overload.⁵⁴ Other indications include residual defects after prior surgical repair, traumatic or iatrogenic defects after surgical aortic valve replacement, patients at high surgical risk, multiple previous cardiac surgical interventions, and poorly accessible muscular VSDs.⁵⁴ Transcatheter VSD closure is not approved by the FDA in the United States for perimembranous VSD.

Devices for Transcatheter Ventricular Septal Defect Closure

There are mainly three devices in use currently for transcatheter VSD closure—the Amplatzer Muscular VSD Occluder, the Amplatzer Membranous VSD Occluder, and the Amplatzer Post Infarction Muscular VSD Occluder (St. Jude Medical) (see Figure 33.4). The latter two are not approved for use in the United States. The Amplatzer Muscular VSD Occluder is a self-expandable, symmetrical double-disk device made from a nitinol wire mesh with a connecting 7-mm-long waist with a diameter corresponding to the size of the VSD. The available waist diameters (and hence device sizes) range from 4 to 18 mm in 2-mm increments. The delivery sheaths range from 6 to 9 Fr in diameter, depending on the device diameter. The Amplatzer Membranous VSD Occluder consists of two disks with a 1.5-mm-long waist. The left-sided disk is asymmetrical, with the aortic end being 0.5 mm larger than the waist and the ventricular end 5.5 mm larger than the waist. The ventricular side of the left-sided disk has a platinum marker to guide proper device deployment. The screw on the right-sided disk has a flat part that should align with the flat part on the capsule of the delivery cable to ensure proper positioning such that the platinum marker on the left-sided disk faces the ventricular apex. The device is available in sizes ranging from 4 to 18 mm in diameter (waist diameter) in 1-mm increments and can be delivered through 7- to 9-Fr sheaths depending on size. The Amplatzer Post Infarction VSD Occluder has two symmetrical disks with a 10-mm-long connecting waist and is available in sizes ranging from 16 to 24 mm in 2-mm increments. It can be delivered via a 9- or 10-Fr sheath, depending on device size.

Contraindications for Closure (Muscular Ventricular Septal Defect)

The Amplatzer Muscular VSD Occluder is contraindicated for use in patients with defects less than 4 mm distance from the aortic, pulmonary, mitral, or tricuspid valve; irreversible pulmonary hypertension, perimembranous or postinfarction VSD; and active endocarditis and in patients with contraindications to antiplatelet agents.

Procedural Details (Muscular Ventricular Septal Defect)

Ventricular septal defect closure is usually performed in the cardiac catheterization laboratory with general anesthesia or conscious sedation and TEE guidance (Video 33.10). The initial steps are similar to those described for ASD closure. Femoral or jugular venous and femoral arterial access is obtained. Generally, VSDs in the upper portion of the septum can be approached from the femoral vein, whereas lower or apical defects may be more amenable to closure by jugular venous approach. Heparin is administered to maintain an ACT greater than 250 seconds, and a dose of intravenous antibiotic is administered before device deployment. Right and left heart catheterization is performed for shunt calculation and assessment of PVR. Biplane left ventriculography is performed (typically in the LAO cranial projection and either straight lateral or orthogonal projection depending on VSD anatomy) to assess the location, size, and number of defects (Figure 33.13). TEE provides additional imaging and guides device placement. The Amplatzer Muscular VSD Occluder chosen should be up to 2 mm larger than the VSD size as assessed by TEE or angiography at end diastole. The VSD is crossed with a guidewire, usually an angled guidewire, using arterial or venous approach (SVC or IVC), depending

on the location of the VSD. After the defect is crossed, the wire is advanced into the pulmonary artery, where it is snared and exteriorized via jugular venous or femoral venous approach, thus creating an arteriovenous loop. Over this exteriorized wire, the delivery sheath and dilator are advanced across the defect from the right to the left ventricle. The delivery cable is passed through the loader, and the Amplatzer Muscular VSD Occluder is attached to the tip of the delivery cable by rotating the device clockwise and rotating one-eighth of a turn counterclockwise at the end. The device and loader are immersed in sterile saline solution, and the device is then retracted into the loader. The dilator and guidewire are then gently removed, allowing for backbleeding to purge air from the system. The loader is then connected to the delivery sheath and advanced to the tip of the delivery sheath. Using TEE and fluoroscopy as a guide, the delivery sheath is slowly retracted to deploy the distal disk. The entire system (delivery sheath and cable) is then pulled into the defect, and then the sheath is retracted to deploy the waist. After positioning is confirmed on echocardiography, angiography, or both, the sheath is then retracted farther to deploy the proximal disk. After appropriate positioning is confirmed, the device is released by rotating the delivery cable counterclockwise until it separates from the device. Echocardiography and angiography are again used to assess the

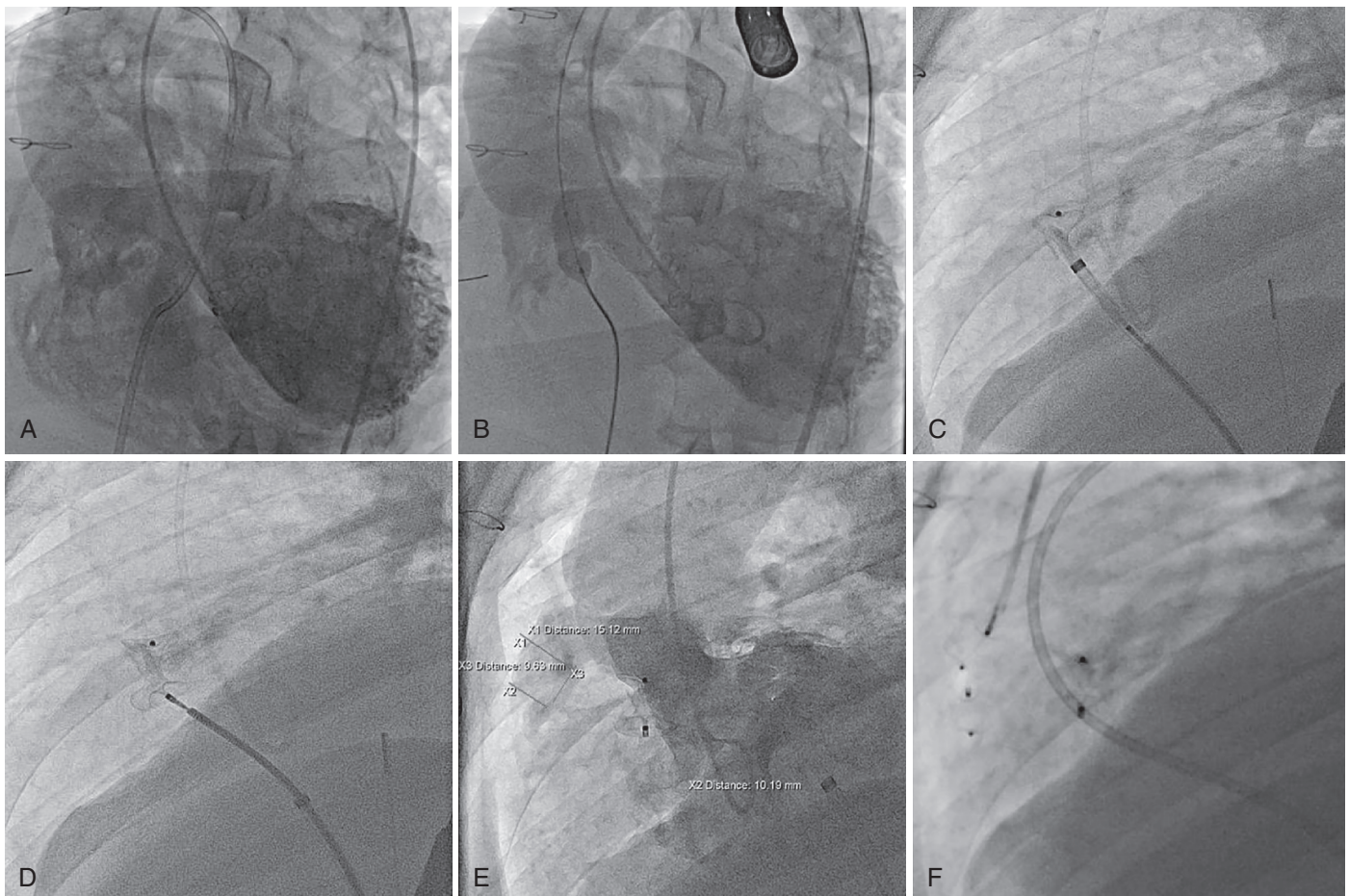


FIGURE 33.13 Fluoroscopic images during transcatheter ventricular septal defects (VSDs) closure. **A**, Left ventriculogram demonstrating VSD patch leak and subaortic VSD. **B**, Sizing balloon. **C** and **D**, Deployment of Amplatzer muscular VSD Occluder. **E**, Left ventriculogram demonstrating second VSD in subaortic position. **F**, Second VSD closed with two Amplatzer vascular plugs.

device, residual shunting and additional lesions if present, and valve function.

Complications

Complications can occur during transcatheter VSD closure. The most common complications include rhythm and conduction disturbances. Complete heart block requiring permanent pacemaker implantation has been reported in 5.7% of patients undergoing percutaneous closure of perimembranous VSD closure.¹²⁷ Other rarer complications include device embolization or migration, pericardial effusion secondary to guidewire perforation, hemolysis, and valvular regurgitation caused by impingement by the device. Snaring techniques can be useful for percutaneous retrieval in case of embolized device. Surgical retrieval should, however, be considered in such cases when there is risk of damaging the atrioventricular valve during percutaneous retrieval.

Clinical Trial Data

Successful VSD closure via the transcatheter route has been reported in 95% to 100% of selected patients.^{128,129} In the multicenter European registry consisting of 430 patients undergoing transcatheter VSD closure, procedural success was achieved in 95% of cases.¹³⁰ In 109 patients undergoing transcatheter perimembranous VSD closure, the rate of procedural success was 96%.¹²⁷ However, the relatively high incidence of complete high block has precluded FDA approval in the United States.

POST-MYOCARDIAL INFARCTION VENTRICULAR SEPTAL DEFECT

The incidence of post-MI VSD has decreased from 1% to 3% to about 0.2% after the advent of emergent reperfusion strategies, including thrombolysis and primary percutaneous coronary intervention.¹³¹ However, mortality rates among patients with post-MI VSD remain high (40%–80%).^{131,132} In contemporary series such as the GUSTO-1 (Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries) and APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) trials, the median time to identification of VSD after MI was less than 24 hours.^{131,133} The risk factors for post-MI VSD include advanced age, female gender, prior stroke, heart failure, and chronic kidney disease.^{132,134} VSD develops after a transmural infarction of the ventricular septum with equal frequency in anterior and inferior/lateral infarctions. Anterior infarctions usually cause apical defects, and inferior/lateral infarctions cause basal defects at the junction of the septum and the posterior wall. The clinical presentation can vary from stability to frank hemodynamic collapse depending on the size of the defect, presence of RV infarction, ongoing RV ischemia, and stunning of the right ventricle from volume overload. Clinically, a harsh systolic murmur or a palpable thrill may be present, but this may be difficult to detect in the presence of cardiogenic shock or low output state. The diagnosis is most often made by

2D echocardiography or by the presence of step-up in oxygen saturation at the ventricular level during right heart catheterization. Left ventriculography in LAO projection should be considered in a patient who continues to be in shock despite emergent revascularization in the catheterization laboratory to evaluate for shunting across the septum.

Management

Management should include prompt revascularization, afterload reduction with sodium nitroprusside and intraaortic balloon pump insertion, and consultation for urgent surgical repair. Definitive surgery is the treatment of choice; however, it is a challenging operation with high early mortality. Surgical repair involves transinfarct ventriculotomy followed by debridement of infarcted tissue and using an appropriately sized patch to avoid tension on the repair. Repair of posterior VSD is more challenging because it requires elevation of the heart for adequate exposure, and the posterior descending artery and the posteromedial papillary muscle are in close proximity. In both anterior and posterior VSDs, the ventriculotomy is closed primarily or with a patch.

A recent review from the STS (Society of Thoracic Surgeons) database showed an operative mortality rate of 43% among 2876 patients who underwent surgical repair for post-MI VSD.¹³⁵ Importantly, mortality rates varied depending on the timing of surgery. Patients who underwent surgery within 7 days of presentation had a mortality rate of 54.1% compared with 18.4% if repair was delayed until after 7 days. This is likely attributable to survival bias. In the early phase, infarcted myocardium is friable and likely to hold sutures poorly, increasing the risk of tearing despite repair. Early surgery is most likely performed in the sickest patients, and better outcomes with delayed surgery may represent evolution of the infarct and increased stability of the tissue, leading to more effective repair. Only 886 of 2876 (30.8%) patients in the STS database had surgery more than 7 days after presentation, suggesting that a minority of patients survive until elective repair. In addition, the number of patients deemed ineligible for surgery is unknown. The GUSTO-1 trial demonstrated 47% mortality rate at 30 days among 34 patients who underwent prompt surgical repair (median time, 3.5 days) compared with a 94% mortality rate in 35 patients who were managed without surgery.¹³¹ Data on the use of extracorporeal membrane oxygenation (ECMO), LV assist device, or Tandem-Heart as bridge to surgery or heart transplant are limited to case reports.¹³⁶⁻¹³⁸ In the absence of large-scale data, the risks of emergent surgery must be balanced against the risk of postponing surgery in a case-by-case fashion using a multidisciplinary team approach.

Transcatheter Post-Myocardial Infarction Ventricular Septal Defect Closure

Transcatheter techniques for closure of post-MI VSD have recently evolved.¹³⁹⁻¹⁴⁴ These have largely been used in patients at very high risk from surgical repair, either as definitive therapy or as a bridge to surgical repair after stabilization.

No specific devices for post-MI VSD closure are available in the United States. Devices used for ASD and muscular VSD closure have been used for post-MI VSD closure. The Amplatzer post-MI VSD Occluder is not approved in the United States (although it is available under Humanitarian Device Exemption use). Several considerations are considered when deciding the type and size of device to be implanted. Typically, a defect smaller than 15 mm in size is considered optimal for transcatheter closure because of the device sizes available and the size of the septum. Inferior and posterior defects are very challenging for transcatheter closure because of a lack of an adequate rim and proximity to the septal leaflet of the tricuspid valve. Additionally, serpiginous defects can also be technically very difficult to close. For the largest Amplatzer ASO device (38 mm), the left-sided disk diameter is 54 mm, whereas for the largest post-MI VSD Occluder (24 mm), the left-sided disk diameter is 32 mm. The left-sided disk diameter for the largest (18 mm) Amplatzer Muscular VSD Occluder available in the United States is 26 mm, which can be too small to fully cover post-MI VSD. The waist lengths range from 4 mm for Amplatzer ASO device to 7 mm for Amplatzer Muscular VSD Occluder and 10 mm for Amplatzer post-MI VSD Occluder. The Amplatzer Cribriform device

has both disks of equal diameter, with fixed short waist length and diameter, and the device size is based on disk diameter (18, 25, 30, and 35 mm). It is important to keep in mind that the necrotic rims of the VSD are often friable, and the guide catheter or wire can tear through the septum while the device is being delivered. Also, a device with wide waist, such as Muscular VSD Occluder or ASO device, can exert pressure on the rims and tear the borders. Because of size, the muscular VSD device may not be sufficient to close the VSD completely. Post-MI VSDs are often complex and tend to have multiple exit points in addition to a thin septum. The Amplatzer Cribriform device can be very helpful if the defects are irregular and multiple when the device is placed from the largest or most central defect (Figure 33.14). Incomplete release of the right-sided disk with persistent shunting has been described with Amplatzer ASO device (cobra phenomenon).¹⁴⁰ Therefore, using a transseptal approach to deploy the right-sided disk first by “pushing it out” may help to prevent this complication as well as prevent tricuspid regurgitation from immobilizing the septal leaflet of tricuspid valve. As healing progresses, the VSD can sometimes enlarge in size, leading to device malapposition or embolization mainly to the right ventricle. Imaging with echocardiography (TTE, TEE, and

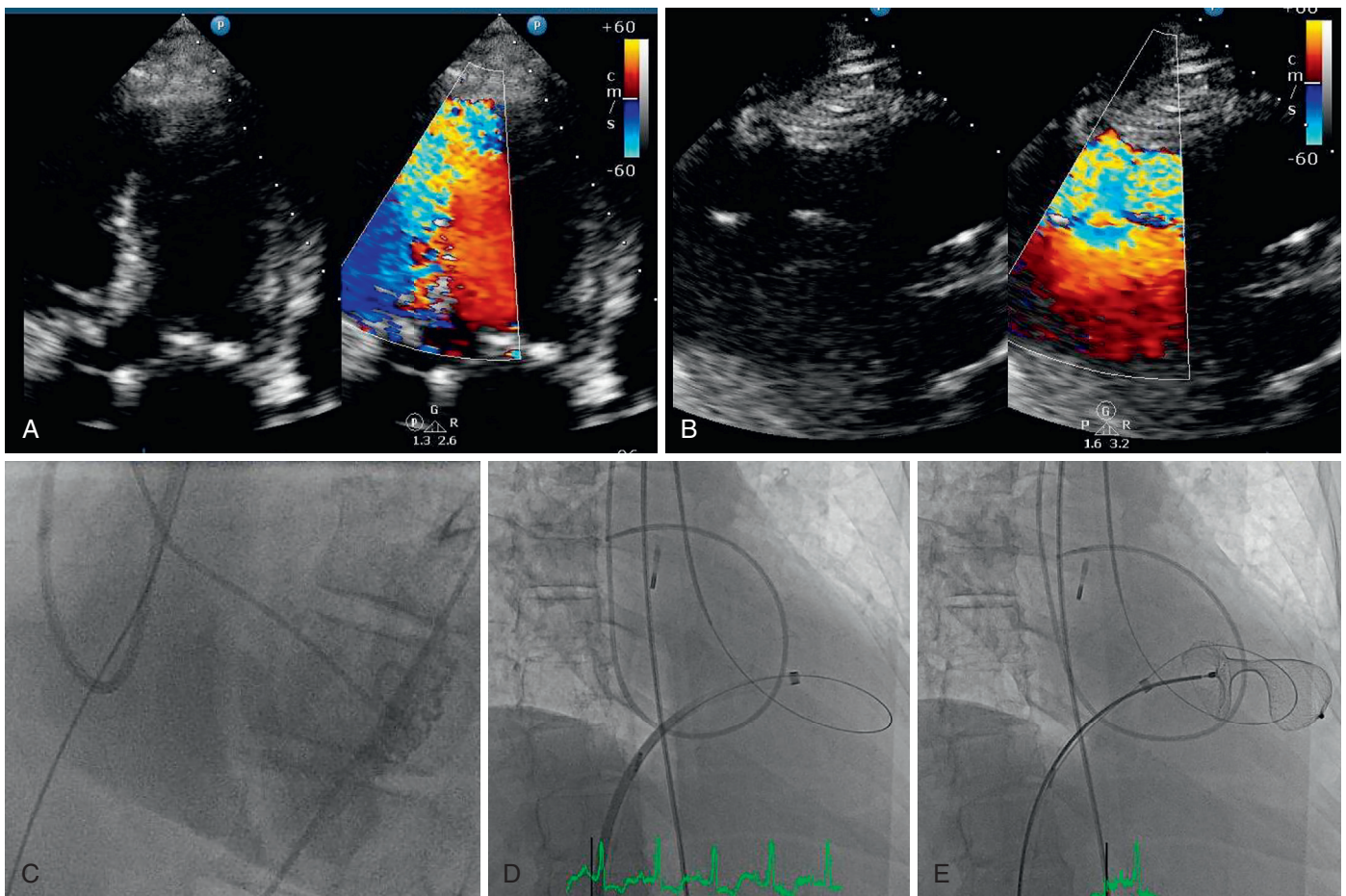


FIGURE 33.14 Transesophageal echocardiography (TEE) demonstrating apical post-myocardial infarction (MI) ventricular septal defect (VSD), and fluoroscopic images during transcatheter post-MI VSD closure using Amplatzer cribriform device. **A** and **B**, Four-chamber and parasternal short axis TTE demonstrating apical post-MI VSD. **C**, Left ventriculogram in LAO projection showing VSD. **D**, Creation of arteriovenous loop through the VSD. **E**, Device deployment across the VSD.

sometimes ICE) is critical in assessing anatomic features to determine feasibility of transcatheter closure and the type and size of device to be used.

A retrograde approach from the aortic valve or a transeptal approach to cross from the mitral valve is preferable depending on the location of the defect. A soft 0.035-inch wire such as a Wholey wire is passed across the defect from the left ventricle to the right ventricle. The wire is then snared in the pulmonary artery via jugular or femoral venous approach and externalized. The authors prefer the femoral venous approach. The delivery sheath can be advanced from the venous side and across the VSD into the left ventricle from the right side or from the LA across the VSD into the right ventricle. The device deployment therefore can be performed from the right ventricle or left ventricle. Both have advantages and disadvantages. The deployment from the transeptal approach can cause hemodynamic instability from mitral regurgitation, whereas the “cobra phenomenon,” or TR, can be potentially less likely from this approach. An alternative approach involves a hybrid procedure wherein the device can be placed under fluoroscopic guidance after an introducer is directly placed in the right atrium or right ventricle after a standard thoracotomy or under direct visualization. The potential advantages of hybrid approach include direct approach, potential sparing of the tricuspid valve (TV), and securing the device with additional sutures or patches. Patients are typically on cardiopulmonary bypass with arrested heart, and the device is deployed with fluoroscopic guidance. This approach obviates the need for left ventriculotomy and repair compared with conventional surgery.

Case series of transcatheter closure of post-MI VSD have reported 30-day mortality rates ranging from 23% to 65%.^{139,140} Transcatheter closure techniques can also be useful in cases of residual leak after primary surgical repair.

There are several challenges in managing patients with post-MI VSD. It is important to discuss in a multidisciplinary fashion (based on hemodynamic status and comorbidities) whether patients are candidates for surgical repair and, if so, the timing of surgery. In stable patients with post-MI VSD, delayed elective surgery may be considered. If patients are not candidates for immediate surgery, transcatheter closure or supportive measures such as ECMO and percutaneous ventricular assist device should be considered. Transcatheter closure may offer an opportunity to stabilize patients who are not candidates for immediate surgical repair, although the data are currently limited. Further developments in device and delivery techniques in conjunction with multicenter studies may be needed to find optimal management strategies for patients with post-MI VSD.

CONCLUSIONS

Patent foramen ovale, ASD, LAA, and VSD closures are evolving rapidly as the field of structural heart intervention matures. Continued improvement in these types of devices, increased technical proficiency, and better adjunctive imaging are making these procedures safer. Ongoing

studies will help refine which specific types of patients benefit most from these technologies. PFO, ASD, LAA, and VSD closures have become an important part of interventional cardiology.

REFERENCES

- Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc.* 1984;59:17-20.
- Schröder R. Indication and techniques of transcatheter closure of patent foramen ovale. *J Interv Cardiol.* 2003;16:543-551.
- Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med.* 2007;357:2262-2268.
- Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med.* 1988;318:1148-1152.
- Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med.* 2001;345(24):1740-1746.
- Lamy C, Giannesini C, Zuber M, et al. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. *Atrial Septal Aneurysm. Stroke.* 2002;33(3):706-711.
- Hara H, Virmani R, Ladich E, et al. Patent foramen ovale: current pathology, pathophysiology, and clinical status. *J Am Coll Cardiol.* 2005;46(9):1768-1776.
- Cramer SC, Rordorf G, Maki JH, et al. Increased pelvic vein thrombi in cryptogenic stroke: results of the Paradoxical Emboli from Large Veins in Ischemic Stroke (PELVIS) study. *Stroke.* 2004;35(1):46-50.
- Meacham RR III, Headley AS, Bronze MS, Lewis JB, Rester MM. Impending paradoxical embolism. *Arch Intern Med.* 1998;158(5):438-448.
- Srivastava TN, Payment MF. Images in clinical medicine. Paradoxical embolism—thrombus in transit through a patent foramen ovale. *N Engl J Med.* 1997;337:681.
- Meier B, Lock JE. Contemporary management of patent foramen ovale. *Circulation.* 2003;107:5-9.
- Cabanes L, Mas JL, Cohen A, et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. *Stroke.* 1993;24(12):1865-1873.
- Guérin P, Lambert V, Godart F, et al. Transcatheter closure of patent foramen ovale in patients with platypnea-orthodeoxia: results of a multicentric French registry. *Cardiovasc Intervent Radiol.* 2005;28(2):164-168.
- Billinger M, Zbinden R, Mordasini R, et al. Patent foramen ovale closure in recreational divers: effect on decompression illness and ischaemic brain lesions during long-term follow-up. *Heart.* 2011;97:1932-1937.
- Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. *Cephalalgia.* 2008;28:531-540.
- Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. *Lancet.* 2000;356:1648-1651.
- Reisman M, Christofferson RD, Jesurum J, et al. Migraine headache relief after transcatheter closure of patent foramen ovale. *J Am Coll Cardiol.* 2005;45(4):493-495.
- Vigna C, Marchese N, Inchingolo V, et al. Improvement of migraine after patent foramen ovale percutaneous closure in patients with subclinical brain lesions: a case-control study. *JACC Cardiovasc Interv.* 2009;2:107-113.
- Rigatelli G, Dell'Avvocata F, Ronco F, et al. Primary transcatheter patent foramen ovale closure is effective in improving migraine in patients with high-risk anatomic and functional characteristics for paradoxical embolism. *JACC Cardiovasc Interv.* 2010;3(3):282-287.
- Desai AJ, Fuller CJ, Jesurum JT, Reisman M. Patent foramen ovale and cerebrovascular diseases. *Nat Clin Pract Cardiovasc Med.* 2006;3:446-455.
- Gin KG, Huckell VF, Pollick C. Femoral vein delivery of contrast medium enhances transthoracic echocardiographic detection of patent foramen ovale. *J Am Coll Cardiol.* 1993;22:1994-2000.
- Hamann GF, Schätzer-Klotz D, Fröhlich G, et al. Femoral injection of echo contrast medium may increase the sensitivity of testing for a patent foramen ovale. *Neurology.* 1998;50(5):1423-1428.
- Goel SS, Tuzcu EM, Shishehbor MH, et al. Morphology of the patent foramen ovale in asymptomatic versus symptomatic (stroke or transient ischemic attack) patients. *Am J Cardiol.* 2009;103(1):124-129.
- Rana BS, Thomas MR, Calvert PA, Monaghan MJ, Hildick-Smith D. Echocardiographic evaluation of patent foramen ovale prior to device closure. *JACC Cardiovasc Imaging.* 2010;3(7):749-760.
- Schneider B, Zienkiewicz T, Jansen V, Hofmann T, Noltenius H, Meinertz T. Diagnosis of patent foramen ovale by transesophageal echocardiography and correlation with autopsy findings. *Am J Cardiol.* 1996;77(14):1202-1209.
- Monte I, Grasso S, Licciardi S, Badano LP. Head-to-head comparison of real-time three-dimensional transthoracic echocardiography with transthoracic and transesophageal two-dimensional contrast echocardiography for the detection of patent foramen ovale. *Eur J Echocardiogr.* 2010;11(3):245-249.
- Nusser T, Höher M, Merkle N, et al. Cardiac magnetic resonance imaging and transesophageal echocardiography in patients with transcatheter closure of patent foramen ovale. *J Am Coll Cardiol.* 2006;48(2):322-329.

28. Hur J, Kim YJ, Lee HJ, et al. Cardiac computed tomographic angiography for detection of cardiac sources of embolism in stroke patients. *Stroke*. 2009;40(6):2073-2078.
29. Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? *Stroke*. 2009;40(7):2349-2355.
30. Dearani JA, Ugurlu BS, Danielson GK, et al. Surgical patent foramen ovale closure for prevention of paradoxical embolism-related cerebrovascular ischemic events. *Circulation*. 1999;100(suppl 19):III171-II175.
31. Kavinsky CJ, Szerlip M, Goldsweig AM, et al. SCAI guidelines for the management of patent foramen ovale. *J Soc Cardiovasc Angiogr Interv*. 2002;1:100039.
32. Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med*. 2001;345(20):1444-1451.
33. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP, PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation*. 2002;105(22):2625-2531.
34. Agarwal S, Bajaj NS, Kumbhani DJ, Tuzcu EM, Kapadia SR. Meta-analysis of transcatheter closure versus medical therapy for patent foramen ovale in prevention of recurrent neurological events after presumed paradoxical embolism. *JACC Cardiovasc Interv*. 2012;5(7):777-789.
35. Elgendy AY, Saver JL, Amin Z, et al. Proposal for updated nomenclature and classification of potential causative mechanism in patent foramen ovale-associated stroke. *JAMA Neurol*. 2020;77(7):878-886.
36. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology*. 2013;81(7):619-625.
37. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med*. 2012;366:991-999.
38. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med*. 2013;368(12):1092-1100.
39. Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med*. 2017;377:1022-1032.
40. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med*. 2013;368(12):1083-1091.
41. Mas JL, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or Anticoagulation vs. Antiplatelets after stroke. *N Engl J Med*. 2017;377:1011-1021.
42. Sondergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med*. 2017;377:1033-1042.
43. Lee PH, Song JK, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. *J Am Coll Cardiol*. 2018;71:2335-2342.
44. Turc G, Calvet D, Guérin P, et al. Closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE study. *J Am Heart Assoc*. 2018;7(12):e008356.
45. Kent DM, Saver JL, Kasner SE, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke. *JAMA*. 2021;326(22):2277-2286. Erratum in: *JAMA*. 2022;327(4):394.
46. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2021;52(7):e364-e467.
47. Dowson A, Mullen MJ, Peatfield R, et al. Migraine Intervention with STARflex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARflex septal repair implant to resolve refractory migraine headache. *Circulation*. 2008;117(11):1397-1404.
48. Tobis JM, Charles A, Silberstein SD, et al. Percutaneous closure of patent foramen ovale in patients with migraine: the PREMIUM trial. *J Am Coll Cardiol*. 2017;70(22):2766-2774.
49. Mattle HP, Evers S, Hildick-Smith D, et al. Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial. *Eur Heart J*. 2016;37(26):2029-2036.
50. Mojaddidi MK, Kumar P, Mahmoud AN, et al. Pooled analysis of PFO occluder device trials in patients with PFO and migraine. *J Am Coll Cardiol*. 2021;77:667-676.
51. Mojaddidi MK, Elgendy AY, Elgendy IY, et al. Transcatheter patent foramen ovale closure after cryptogenic stroke: an updated meta-analysis of randomized trials. *JACC Cardiovasc Interv*. 2017;10:2228-2230.
52. Goel SS, Aksoy O, Tuzcu EM, Krasuski RA, Kapadia SR. Embolization of patent foramen ovale closure devices: incidence, role of imaging in identification, potential causes, and management. *Tex Heart Inst J*. 2013;40:439-444.
53. Kumar P, Orford JL, Tobis JM. Two cases of pericardial tamponade due to nitinol wire fracture of a gore septal occluder. *Catheter Cardiovasc Interv*. 2020;96:219-224.
54. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC Guideline for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;73(12):e81-e192.
55. Murphy JG, Gersh BJ, McGoon MD, et al. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. *N Engl J Med*. 1990;323(24):1645-1650.
56. Gatzoulis MA, Freeman MA, Siu SC, Webb GD, Harris L. Atrial arrhythmia after surgical closure of atrial septal defects in adults. *N Engl J Med*. 1999;340:839-846.
57. Sommer RJ, Love BA, Paolillo JA, et al. ASSURED clinical study: new GORE® CARDIOFORM ASD occluder for transcatheter closure of atrial septal defect. *Catheter Cardiovasc Interv*. 2020;95:1285-1295.
58. Kutty S, Asnes JD, Srinath G, et al. Use of a straight, side-hole delivery sheath for improved delivery of Amplatzer ASD occluder. *Catheter Cardiovasc Interv*. 2007;69:15-20.
59. Dalvi BV, Pinto RJ, Gupta A. New technique for device closure of large atrial septal defects. *Catheter Cardiovasc Interv*. 2005;64:102-107.
60. Lurz P, Unterhuber M, Rommel K-P, et al. Iatrogenic atrial septal defects following transcatheter mitral valve repair and implications of interventional closure. *JACC Cardiovasc Interv*. 2021;14(24):2685-2694.
61. Du Z-D, Hijazi ZM, Kleinman CS, Silverman NH, Lantzt K, Amplatzer Investigators. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. *J Am Coll Cardiol*. 2002;39:1836-1844.
62. Jones TK, Latson LA, Zahn E, et al. Results of the U.S. multicenter pivotal study of the HELEX septal occluder for percutaneous closure of secundum atrial septal defects. *J Am Coll Cardiol*. 2007;49:2215-2221.
63. Amin Z, Hijazi ZM, Bass JL, Cheatham JP, Hellenbrand WE, Kleinman CS. Erosion of Amplatzer septal occluder device after closure of secundum atrial septal defects: review of registry of complications and recommendations to minimize future risk. *Catheter Cardiovasc Interv*. 2004;63:496-502.
64. Crawford GB, Brindis RG, Krucoff MW, Mansalis BP, Carroll JD. Percutaneous atrial septal occluder devices and cardiac erosion: a review of the literature. *Catheter Cardiovasc Interv*. 2012;80:157-167.
65. El-Said HG, Moore JW. Erosion by the Amplatzer septal occluder: experienced operator opinions at odds with manufacturer recommendations? *Catheter Cardiovasc Interv*. 2009;73:925-930.
66. McElhinney DB, Quartermain MD, Kenny D, Alboliras E, Amin Z. Relative risk factors for cardiac erosion following transcatheter closure of atrial septal defects: a case-control study. *Circulation*. 2016;133:1738-1746.
67. Levi DS, Moore JW. Embolization and retrieval of the Amplatzer septal occluder. *Catheter Cardiovasc Interv*. 2004;61:543-547.
68. DiBardino DJ, McElhinney DB, Kaza AK, Mayer JE Jr. Analysis of the US Food and Drug Administration Manufacturer and User Facility Device Experience database for adverse events involving Amplatzer septal occluder devices and comparison with the Society of Thoracic Surgery congenital cardiac surgery database. *J Thorac Cardiovasc Surg*. 2009;137:1334-1341.
69. Masura J, Gavora P, Podnar T. Long-term outcome of transcatheter secundum-type atrial septal defect closure using Amplatzer septal occluders. *J Am Coll Cardiol*. 2005;45:505-507.
70. Fischer G, Stieh J, Uebing A, Hoffmann U, Morf G, Kramer HH. Experience with transcatheter closure of secundum atrial septal defects using the Amplatzer septal occluder: a single centre study in 236 consecutive patients. *Heart*. 2003;89:199-204.
71. Gillespie MJ, Javois AJ, Moore P, Forbes T, Paolillo JA, GSO Investigator Group. Use of the GORE® CARDIOFORM Septal Occluder for percutaneous closure of secundum atrial septal defects: results of the multicenter U.S. IDE trial. *Catheter Cardiovasc Interv*. 2020;95:1296-1304.
72. Butera G, Carminati M, Chessa M, et al. Percutaneous versus surgical closure of secundum atrial septal defect: comparison of early results and complications. *Am Heart J*. 2006;151:228-234.
73. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18-e209.
74. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983-988.
75. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864-2870.
76. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA*. 2003;290:2685-2692.
77. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857-867.
78. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903-1912.
79. Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. *Arch Intern Med*. 2007;167:1414-1419.
80. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? *Arch Intern Med*. 2000;160:41-46.
81. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139-1151.
82. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation*. 2011;123:2363-2372.
83. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981-992.

84. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in non-valvular atrial fibrillation. *N Engl J Med*. 2011;365:883-891.
85. Veinot JP, Harrity PJ, Gentile F, et al. Anatomy of the normal left atrial appendage: a quantitative study of age-related changes in 500 autopsy hearts: implications for echocardiographic examination. *Circulation*. 1997;96:3112-3115.
86. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg*. 1996;61:755-759.
87. Gillinov AM, Pettersson G, Cosgrove DM. Stapled excision of the left atrial appendage. *J Thorac Cardiovasc Surg*. 2005;129:679-680.
88. Healey JS, Crystal E, Lamy A, et al. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. *Am Heart J*. 2005;150:288-293.
89. Kanderian AS, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. *J Am Coll Cardiol*. 2008;52:924-929.
90. Whitlock RP, Belley-Cote EP, Paparella D, et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. *N Engl J Med*. 2021;384:2081-2091.
91. Krishnaswamy A, Patel NS, Ozkan A, et al. Planning left atrial appendage occlusion using cardiac multidetector computed tomography. *Int J Cardiol*. 2012;158:313-317.
92. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009;374:534-542.
93. Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA*. 2014;312:1988-1998.
94. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*. 2014;64:1-12.
95. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation*. 2011;123:417-424.
96. Reddy VY, Möbius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol*. 2013;61:2551-2556.
97. Boersma LV, Ince H, Kische S, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm*. 2017;14:1302-1308.
98. Freeman JV, Varosy P, Price MJ, et al. The NCDR Left Atrial Appendage Occlusion Registry. *J Am Coll Cardiol*. 2020;75:1503-1518.
99. Kar S, Doshi SK, Sadhu A, et al. Primary outcome evaluation of a next-generation left atrial appendage closure device: results from the PINNACLE FLX Trial. *Circulation*. 2021;143:1754-1762.
100. Kapadia S. *Late Breaking Clinical Trial at CRT*. 2022.
101. Viles-Gonzalez JF, Kar S, Douglas P, et al. The clinical impact of incomplete left atrial appendage closure with the watchman device in patients with atrial fibrillation: a PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation) substudy. *J Am Coll Cardiol*. 2012;59:923-929.
102. Dukkipati SR, Holmes DR Jr, Doshi SK, et al. Impact of peridevice leak on 5-year outcomes after left atrial appendage closure. *J Am Coll Cardiol*. 2022;80:469-483.
103. Sleiman JR, Lewis AJ, Perez EJ, et al. Management of peri-device leak following left atrial appendage closure: a systematic review. *Catheter Cardiovasc Interv*. 2021;98:382-390.
104. Saw J, Nielsen-Kudsk JE, Bergmann M, et al. Antithrombotic therapy and device-related thrombosis following endovascular left atrial appendage closure. *JACC Cardiovasc Interv*. 2019;12:1067-1076.
105. Bergmann MW, Ince H, Kische S, et al. Real-world safety and efficacy of WATCHMAN LAA closure at one year in patients on dual antiplatelet therapy: results of the DAPT subgroup from the EWOLUTION all-comers study. *EuroIntervention*. 2018;13:2003-2011.
106. Landmesser U, Schmidt B, Nielsen-Kudsk JE, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. *EuroIntervention*. 2017;13:867-876.
107. Simard T, Jung RG, Lehenbauer K, et al. Predictors of device-related thrombus following percutaneous left atrial appendage occlusion. *J Am Coll Cardiol*. 2021;78:297-313.
108. Kubo S, Mizutani Y, Meemook K, et al. Incidence, characteristics, and clinical course of device-related thrombus after Watchman left atrial appendage occlusion device implantation in atrial fibrillation patients. *JACC Clin Electrophysiol*. 2017;3:1380-1386.
109. Park JW, Bethencourt A, Sievert H, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. *Catheter Cardiovasc Interv*. 2011;77:700-706.
110. Nietlispach F, Gloekler S, Krause R, et al. Amplatzer left atrial appendage occlusion: single center 10-year experience. *Catheter Cardiovasc Interv*. 2013;82:283-289.
111. Tzikas A, Shakir S, Gafoor S, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. *EuroIntervention*. 2016;11:1170-1179.
112. Landmesser U, Tondo C, Camm J, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: one-year follow-up from the prospective global Amulet observational registry. *EuroIntervention*. 2018;14:e590-e597.
113. Galea R, De Marco F, Meneveau N, et al. Amulet or Watchman device for percutaneous left atrial appendage closure: primary results of the SWISS-APERO randomized clinical trial. *Circulation*. 2022;145:724-738.
114. Lakkireddy D, Thaler D, Ellis CR, et al. Amplatzer Amulet left atrial appendage occluder versus Watchman Device for stroke prophylaxis (Amulet IDE): a randomized, controlled trial. *Circulation*. 2021;144:1543-1552.
115. Osmancik P, Herman D, Neuzil P, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol*. 2020;75:3122-3135.
116. Osmancik P, Herman D, Neuzil P, et al. 4-year outcomes after left atrial appendage closure versus nonwarfarin oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol*. 2022;79:1-14.
117. Bartus K, Han FT, Bednarek J, et al. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. *J Am Coll Cardiol*. 2013;62:108-118.
118. Massumi A, Chelu MG, Nazeri A, et al. Initial experience with a novel percutaneous left atrial appendage exclusion device in patients with atrial fibrillation, increased stroke risk, and contraindications to anticoagulation. *Am J Cardiol*. 2013;111:869-873.
119. Stone D, Byrne T, Pershad A. Early results with the LARIAT device for left atrial appendage exclusion in patients with atrial fibrillation at high risk for stroke and anticoagulation. *Catheter Cardiovasc Interv*. 2015;86:121-127.
120. Greenbaum AB, Rogers T, Paone G, et al. Intentional right atrial exit and carbon dioxide insufflation to facilitate subxiphoid needle entry into the empty pericardial space: first human experience. *JACC Clin Electrophysiol*. 2015;1:434-441.
121. Gunda S, Reddy M, Pillarisetti J, et al. Differences in complication rates between large bore needle and a long micropuncture needle during epicardial access: time to change clinical practice? *Circ Arrhythm Electrophysiol*. 2015;8:890-895.
122. Hoffman JIE, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39:1890-1900.
123. Gersony WM, Hayes CJ. Bacterial endocarditis in patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. *Circulation*. 1993;87:1121-1126.
124. Ellis JH, Moodie DS, Sterba R, Gill CC. Ventricular septal defect in the adult: natural and unnatural history. *Am Heart J*. 1987;114:115-120.
125. Otterstad JE, Erikssen J, Frøysaker T, Simonsen S. Long term results after operative treatment of isolated ventricular septal defect in adolescents and adults. *Acta Med Scand Suppl*. 1986;708:1-39.
126. Kidd L, Driscoll DJ, Gersony WM, et al. Second natural history study of congenital heart defects. Results of treatment of patients with ventricular septal defects. *Circulation*. 1993;87:138-151.
127. Butera G, Carminati M, Chessa M, et al. Transcatheter closure of perimembranous ventricular septal defects: early and long-term results. *J Am Coll Cardiol*. 2007;50:1189-1195.
128. Fu YC, Bass J, Amin Z, et al. Transcatheter closure of perimembranous ventricular septal defects using the new Amplatzer membranous VSD occluder: results of the U.S. phase I trial. *J Am Coll Cardiol*. 2006;47:319-325.
129. Arora R, Trehan V, Thakur AK, Mehta V, Sengupta PP, Nigam M. Transcatheter closure of congenital muscular ventricular septal defect. *J Interv Cardiol*. 2004;17:109-115.
130. Carminati M, Butera G, Chessa M, et al. Transcatheter closure of congenital ventricular septal defects: results of the European Registry. *Eur Heart J*. 2007;28:2361-2368.
131. Crenshaw BS, Granger CB, Birnbaum Y, et al. Risk factors, angiographic patterns, and outcomes in patients with ventricular septal defect complicating acute myocardial infarction. GUSTO-I (Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries) trial investigators. *Circulation*. 2000;101:27-32.
132. Moreyra AE, Huang MS, Wilson AC, et al. Trends in incidence and mortality rates of ventricular septal rupture during acute myocardial infarction. *Am J Cardiol*. 2010;106:1095-1100.
133. French JK, Hellkamp AS, Armstrong PW, et al. Mechanical complications after percutaneous coronary intervention in ST-elevation myocardial infarction (from APEX-AMI). *Am J Cardiol*. 2010;105:59-63.
134. Menon V, Webb JG, Hillis LD, et al. Outcome and profile of ventricular septal rupture with cardiogenic shock after myocardial infarction: a report from the SHOCK Trial Registry. Should we emergently revascularize Occluded Coronaries in cardiogenic shock? *J Am Coll Cardiol*. 2000;36:1110-1116.
135. Arnaoutakis GJ, Zhao Y, George TJ, Sciortino CM, McCarthy PM, Conte JV. Surgical repair of ventricular septal defect after myocardial infarction: outcomes from The Society of Thoracic Surgeons national database. *Ann Thorac Surg*. 2012;94:436-443; discussion 443-444.
136. Loyalka P, Cevik C, Nathan S, Gregoric ID, Kar B. Closure of post-myocardial infarction ventricular septal defect with use of intracardiac echocardiographic imaging and percutaneous left ventricular assistance. *Tex Heart Inst J*. 2012;39:454-456.
137. Tsai MT, Wu HY, Chan SH, Luo CY. Extracorporeal membrane oxygenation as a bridge to definite surgery in recurrent postinfarction ventricular septal defect. *ASAIO J*. 2012;58:88-89.

138. Kar B, Gregoric ID, Basra SS, Idelchik GM, Loyalka P. The percutaneous ventricular assist device in severe refractory cardiogenic shock. *J Am Coll Cardiol*. 2011;57:688-696.
139. Assenza GE, McElhinney DB, Valente AM, et al. Transcatheter closure of post-myocardial infarction ventricular septal rupture. *Circ Cardiovasc Interv*. 2013;6:59-67.
140. Thiele H, Kaulfersch C, Daehnert I, et al. Immediate primary transcatheter closure of postinfarction ventricular septal defects. *Eur Heart J*. 2009;30:81-88.
141. Maltais S, Ibrahim R, Basmadjian A-J, et al. Postinfarction ventricular septal defects: towards a new treatment algorithm? *Ann Thorac Surg*. 2009;87:687-692.
142. Białkowski J, Szkutnik M, Zembala M. [Ventricular septal defect closure—importance of cardiac surgery and transcatheter intervention]. *Kardiologia Pol*. 2007;65:1022-1024.
143. Demkow M, Ruzyllo W, Kepka C, et al. Primary transcatheter closure of postinfarction ventricular septal defects with the Amplatzer septal occluder—immediate results and up-to 5 years follow-up. *EuroIntervention*. 2005;1:43-47.
144. Holzer R, Balzer D, Amin Z, et al. Transcatheter closure of postinfarction ventricular septal defects using the new Amplatzer muscular VSD occluder: results of a U.S. Registry. *Catheter Cardiovasc Interv*. 2004;61:196-201.



34

Interventions For Advanced Heart Failure

NAVIN K. KAPUR, MICHELE L. ESPOSITO, AND MARWAN F. JUMEAN

DISCLOSURE, 626

INTRODUCTION, 626

DEFINING ADVANCED HEART FAILURE, 626

HEMODYNAMICS OF HEART FAILURE, 627

PERCUTANEOUS MECHANICAL CIRCULATORY SUPPORT, 629

Intraaortic Balloon Pump Counterpulsation, 631
Percutaneous Rotodynamic Pumps, 632

CIRCULATORY SUPPORT FOR CARDIOGENIC SHOCK AND ADVANCED HEART FAILURE, 634

INTERVENTIONAL THERAPY FOR RIGHT HEART FAILURE, 636

Emerging Percutaneous Circulatory Support Devices, 639

PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH HEART FAILURE, 640

VALVULAR INTERVENTIONS IN ADVANCED HEART FAILURE, 641

Transcatheter Aortic Valve Replacement in Advanced Heart Failure, 641
Percutaneous Approaches for Functional Mitral Regurgitation, 643

Percutaneous Approaches for Tricuspid Valve Interventions, 644

EMERGING INTERVENTIONAL APPROACHES FOR HEART FAILURE, 645

Percutaneous Ventricular Volume

Reduction, 645

Interventions for Heart Failure with Preserved Ejection Fraction, 645

Novel Device-Based Approaches for Acutely Decompensated Heart Failure, 645

CONCLUSIONS, 646

DISCLOSURE

Dr. Kapur has received preclinical research support from HeartWare Inc. and CardiacAssist Inc. and has worked as a speaker and consultant for Maquet and Thoratec Inc.

INTRODUCTION

Over the past 50 years, pharmacologic advances for cardiovascular risk factors and device innovation for the management of coronary disease, including acute myocardial infarction (AMI), have radically changed the landscape of heart disease. No longer is AMI considered a terminal event because in-hospital mortality rates have been reduced to less than 10%, and more individuals are now surviving their incidents and subsequent heart attacks. However, nearly 25% of individuals develop chronic heart failure after an AMI, leading to a growing number of patients with heart failure entering catheterization laboratories.^{1,2}

An estimated 2.6% of the total American population and nearly 11% of the older adult population older than age 80 years have heart failure, which is defined as “a syndrome caused by cardiac dysfunction, generally resulting from myocardial muscle dysfunction or loss and characterized by either LV [left ventricular] dilation or hypertrophy or both.”³ Of the 10.5 million emergency department visits for acute heart failure each year, nearly 50% occur in patients with preserved systolic function. By 2030, more than 8 million people in the United States (1 in every 33) will be diagnosed with heart failure. Direct and indirect costs for heart failure are projected to increase from \$31 billion in 2012 to \$70 billion in 2030.⁴ The increasing population of individuals with heart failure has also

increased the number of coronary and noncoronary procedures being performed in patients with high-risk features, including advanced age, low ejection fraction, renal insufficiency, and decompensated hemodynamics. The approach to this high-risk interventional population now requires a better understanding of their heart failure status. There exists a growing demand for operators trained in invasive hemodynamics who can interface with an advanced heart failure program inclusive of mechanical support and cardiac transplantation and who have experience with emerging cutting-edge techniques for the management of patients with heart failure.

DEFINING ADVANCED HEART FAILURE

Symptoms of heart failure may occur secondary to disease of the myocardium, endocardium, pericardium, cardiac valves, systemic vasculature, and metabolic or neurohormonal stress. Several classification systems for heart failure exist. First, heart failure can be broadly categorized as being associated with reduced (HFrEF; left ventricular ejection fraction [LVEF] $\leq 40\%$), midrange (HFmEF; LVEF 41%–49%), or preserved (HFpEF; LVEF $\geq 50\%$) LV ejection. Second, the New York Heart Association (NYHA) functional classification categorizes patients based on symptom severity (Table 34.1). Third, the American College of Cardiology (ACC) and the American Heart Association (AHA) have defined progressive stages of heart failure with specific goals and strategies to facilitate management at each level of heart failure (see Table 34.1). Fourth, the term “advanced heart failure” is often reserved for stage D patients who exhibit symptoms refractory to guideline-based management strategies. The European Society of

TABLE 34.1 Heart Failure Definition, Stages, and New York Heart Association Classifications

	INITIAL HEART FAILURE CLASSIFICATION BASED ON LVEF	SERIAL ASSESSMENT AND RECLASSIFICATION
Heart failure definition based on ejection fraction	HFrEF: LVEF $\leq 40\%$ HFmrEF: LVEF 41%–49% HFpEF: LVEF $\geq 50\%$	HFrEF: LVEF $\leq 40\%$ HFimpEF: LVEF $>40\%$ HFrEF: LVEF $<40\%$ HFmrEF: LVEF 41%–49% Not defined: LVEF $\geq 50\%$ HFrEF: LVEF $<40\%$ HFmrEF: LVEF 41%–49% HFpEF: LVEF $\geq 50\%$
ACC/AHA heart failure stages	Stage A: at risk for HF but without evidence of structural heart disease or HF symptoms Stage B: structural heart disease but without signs or symptoms of HF Stage C: structural heart disease with prior or current symptoms of HF Stage D: refractory HF requiring specialized interventions	
NYHA classification	Class I: no limitations to physical activity; no symptoms of HF with ordinary activity Class II: slight limitation to physical activity; symptoms of HF with ordinary activity Class III: marked limitation to physical activity; symptoms of HF with less than ordinary exertion Class IV: inability to carry out any physical activity; symptoms of HF at rest	
ESC definition of heart failure	Diagnosis of HFrEF requires the following three conditions to be satisfied Diagnosis of HFpEF requires the following four conditions to be satisfied	Symptoms typical of HF Signs typical of HF Reduced LVEF Symptoms typical of HF Signs typical of HF Normal or only mildly reduced LVEF, nondilated LV Relevant structural heart disease: LV hypertrophy, LA enlargement, or diastolic dysfunction

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

TABLE 34.2 Definition of Advanced Heart Failure

Markers of advanced heart failure (ACC/AHA)	- Two or more hospitalizations or ED visits for HF in the past 12 mo - Persistent NYHA class IV symptoms - Progressive weight loss - Hypotension - Inability to tolerate ACE inhibitors or beta-blockers, increasing diuretic dose - Progressive decline in renal function - Progressive hyponatremia - Frequent ICD shocks
ESC definition of advanced heart failure	All the following criteria must be present despite optimal medical treatment: - Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV]. - Severe cardiac dysfunction defined by at least one of the following: - LVEF $\leq 30\%$ - Isolated RV failure - Non-operable severe valve abnormalities - Non-operable severe congenital abnormalities - Persistently high or increasing brain natriuretic peptide (BNP) or NT-pro-BNP values and severe LV diastolic dysfunction or structural abnormalities (according to the definitions of HFpEF) - Episodes of pulmonary or systemic congestion requiring high doses intravenous diuretics or diuretic combinations or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months unplanned visit or hospitalization in the last 12 months. - Severe impairment of exercise capacity with inability to exercise or low 6 minute walk test (6MWT) distance ($<300\text{m}$) or peak oxygen consumption ($p\text{VO}_2$) $<12\text{mL/kg/min}$ or $<50\%$ predicted value, estimated to be of cardiac origin.

6MWT, 6-minute walk test; ACC, American College of Cardiology; ACE, angiotensin-converting enzyme; AHA, American Heart Association; ARVC, arrhythmogenic right ventricular cardiomyopathy; BNP, B-type natriuretic peptide; ED, emergency department; EF, ejection fraction; ESC, European Society of Cardiology; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter defibrillator; IV, intravenous; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; $p\text{VO}_2$, peak oxygen consumption; RV, right ventricular; VO_2 , oxygen consumption.

Cardiology has defined advanced heart failure using several criteria (Table 34.2). For stage D patients being considered for surgical ventricular assist devices, the Interagency for Mechanically Assisted Circulatory Support (INTERMACS) has further defined distinct patient profiles for risk stratification (Table 34.3).⁵⁻⁷

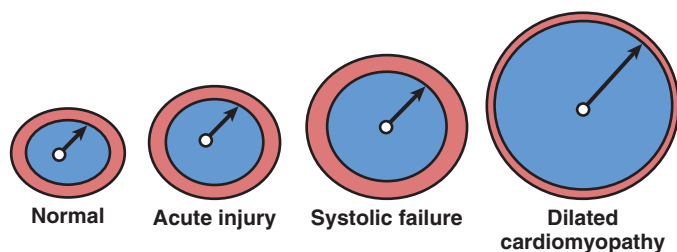
HEMODYNAMICS OF HEART FAILURE

Nearly all approaches to treat heart failure reduce ventricular wall stress, which is defined by the law of Laplace as the product of ventricular pressure and volume and is inversely related to wall thickness (Figure 34.1). Across all

TABLE 34.3 INTERMACS Profiles, Updated Version

INTERMACS PATIENT PROFILE NUMBER	DEFINITION
1	Critical cardiogenic shock despite escalating support
2	Progressive decline despite inotropes
3	Clinically stable but inotrope dependent
4	Recurrent, not refractory, advanced heart failure
5	Exertion intolerant; comfortable at rest
6	Exertion limited; can perform mild activity
7	Advanced NYHA class III

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NYHA, New York Heart Association.



$$\text{Wall stress} = \frac{\text{Pressure} \times \text{Radius}}{2 \times \text{Wall thickness}} = \frac{\text{ESP} \times \text{EDV}}{\text{LV mass}}$$

FIGURE 34.1 Hemodynamics of heart failure. *Cardiac remodeling* is a term that broadly refers to changes in myocardial structure and function in response to injury. Irrespective of the injurious mechanism (i.e., myocardial infarction, hypertensive heart disease, valvulopathy, myocarditis, or primary myocyte failure), a decline in ventricular function activates the sympathetic nervous system and the renin-angiotensin-aldosterone system, which increase left ventricular end-systolic pressure (ESP) and end-diastolic pressure (EDP). Sustained neurohormonal activation promotes systolic failure and can lead to a dilated cardiomyopathy, where left ventricle end-diastolic volume (EDV) is increased. Ventricular afterload is defined as wall stress generated during systolic ejection. The law of Laplace quantifies ventricular wall stress, which can be represented as the product of ESP and EDV. LV, Left ventricular.

phases of heart failure progression, from an inciting event (i.e., myocardial infarction [MI]) to chronic dilated cardiomyopathy, increased LV pressure and volume promotes LV wall stress. Increased wall stress, in turn, activates adaptive signaling cascades that stimulate myocardial hypertrophy, fibrosis, and inflammation, which over time can result in maladaptive remodeling of the heart. Both pharmacologic and mechanical therapies for heart failure limit LV wall stress by reducing LV volume and pressure.

The hemodynamics of heart failure and the effect of therapeutic interventions can be represented in the pressure-volume (PV) domain using data derived from a conductance catheter. Each PV loop represents one cardiac cycle (Figure 34.2). Various pharmacologic interventions, such as increasing preload with volume resuscitation, increasing afterload with vasopressors, and increasing inotropy, modulate ventricular PV relationships differently. In most cases, these interventions are adequate to stabilize hemodynamics, augment native stroke volume, and increase vital organ perfusion. However, over time, persistent exposure to increased ventricular load worsens LV wall stress (Figure 34.3), which increases myocardial oxygen

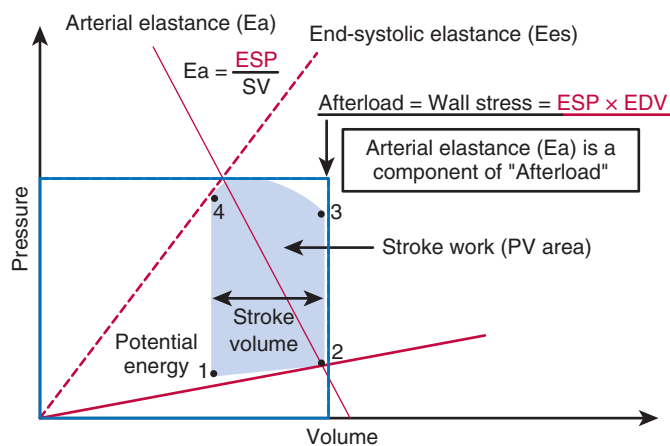


FIGURE 34.2 Cardiac hemodynamics in the pressure-volume (PV) domain. Each PV loop represents one cardiac cycle. Beginning at the end of isovolumic relaxation (1), left ventricular (LV) volume increases during diastole (phase 1 to 2). At end-diastole (2), LV volume is maximal, and isovolumic contraction (phase 2 to 3) begins. At the peak of isovolumic contraction, LV pressure exceeds aortic pressure, and blood begins to eject from the LV into the aorta (3). During this systolic ejection phase, LV volume decreases until aortic pressure exceeds LV pressure and the aortic valve closes, which is known as the end-systolic pressure-volume point (ESPV) (4). Stroke volume (SV) is represented by the width of the PV loop as the difference between end-systolic volume (ESV) and end-diastolic volume (EDV) (point 1—2). Load-independent contractility, also known as elastance at end-systole (Ees), is defined as the maximal slope of the ESPV point under various loading conditions, known as the ESPV relationship (ESPVR). Effective arterial elastance (Ea) is defined as the ratio of end-systolic pressure (ESP) and SV. Under steady-state conditions, optimal LV pump efficiency occurs when the ratio of Ea:Emax approaches. Arterial elastance is a component of afterload, which is defined as the resistance to LV ejection throughout systole and can be represented as the product of ESP and EDV.

demand and promotes myocardial ischemia and can trigger ventricular arrhythmias.

In 1914, Ernest Starling extended findings from Otto Frank and defined the Frank-Starling mechanism, which describes the intrinsic ability of the heart to increase stroke volume in response to increases in LV pressure or volume. Numerous studies have confirmed these early observations and further showed that in heart failure, the slope of the operating curve defined by LV pressure and volume is reduced, and small changes in LV pressure or volume can lead to hypotension or pulmonary congestion (Figure 34.4). At each of these stages (acute heart failure, stable chronic heart failure, and decompensated heart failure or cardiogenic shock [CS]), the objectives of therapy

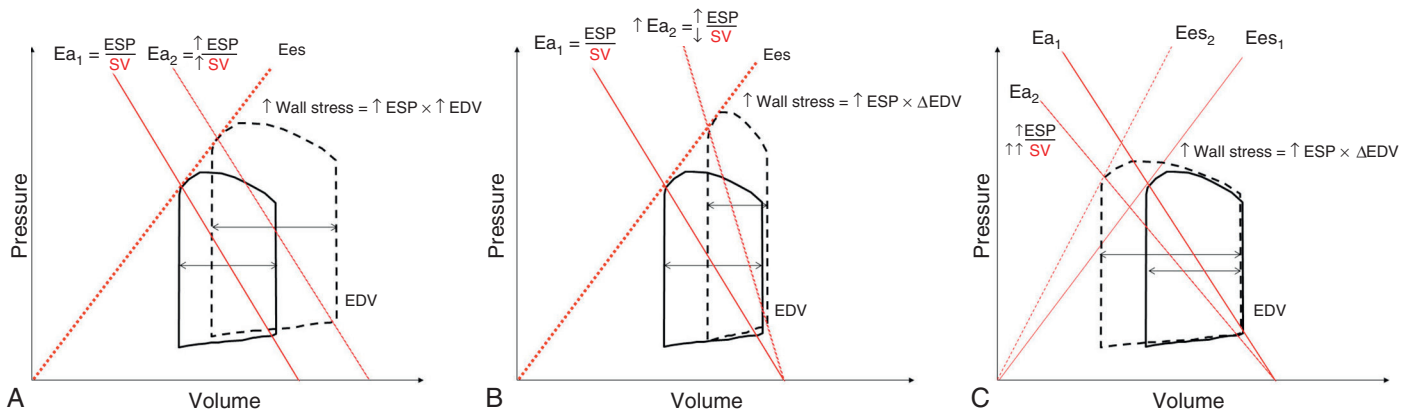


FIGURE 34.3 Impact of modulating preload, afterload, and inotropy on pressure-volume relationships in the left ventricle. **A**, Increasing preload augments left ventricular (LV) stroke volume (SV; horizontal arrows) and increases both end-systolic pressure (ESP) and end-diastolic volume (EDV) without changing elastance at end-systole (Ees) or arterial elastance (Ea). The net effect is increased LV wall stress (i.e., afterload) caused by increased ESP and EDV. **B**, Vasopressors increase ESP and reduce SV without affecting EDV or Ees. Both Ea and LV wall stress are increased because of elevated ESP. **C**, Inotropes increase myocardial contractility (Ees), ESP, and SV without affecting EDV. Ea is decreased because of increased SV, but LV wall stress is increased because of increased ESP. Inotropes also increase heart rate and promote myocardial oxygen demand. Solid lines represent baseline conditions. Dashed lines represent modulated conditions.

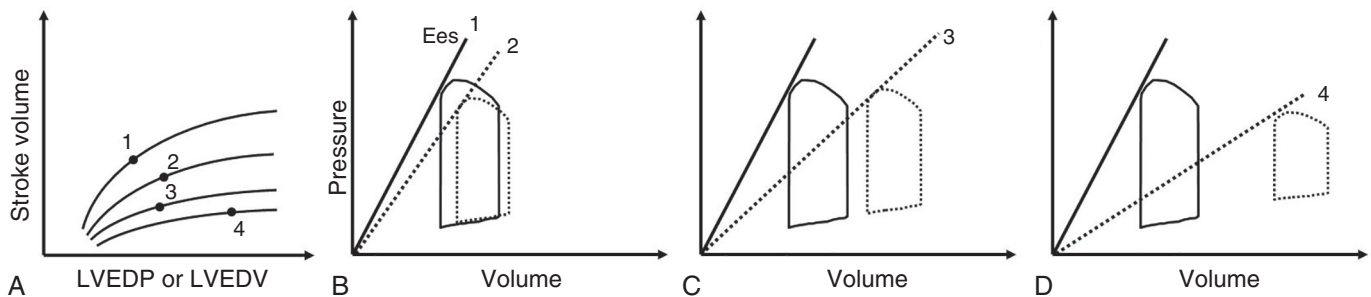


FIGURE 34.4 Hemodynamic conditions associated with stages of cardiac injury and treatment profiles. **A**, Frank-Starling curves represent the relationship (slope) between stroke volume (SV) (or cardiac output) and left ventricular end-diastolic pressure or end-diastolic volume (LVEDP or LVEDV). **B–D**, Pressure-volume (PV) loops represent the relationship between left ventricular (LV) pressure and LV volume. **A–D**, Resting conditions are represented by slope 1 and solid-lined PV loops. Increased LVEDP or LVEDV is associated with increased SV. **B**, Acute cardiac injury reduces the Frank-Starling curve (slope 2) and elastance at end-systole (Ees; dashed line) and increases end-diastolic volume and pressure. **C**, Chronic systolic heart failure is associated with a reduced Frank-Starling curve (slope 3) and Ees. Patients with compensated systolic heart failure may demonstrate preserved SV (width of the PV loop), increased LVEDV, and normal or mildly increased LVEDP. Increased LVEDP or LVEDV is associated with small increases in SV. **D**, Decompensated systolic heart failure or cardiogenic shock is associated with reduced Ees and a flat Frank-Starling curve (slope 4). In this condition, increased LVEDP or LVEDV is not associated with increased SV.

are to improve stroke volume and reduce intracardiac volume and pressure overload while maintaining an adequate mean arterial pressure (MAP) to support end-organ tissue perfusion. For these reasons, careful timing and selection of pharmacologic therapy can impact patient outcomes. Invasive diagnostic evaluation and monitoring can guide therapy in advanced heart failure management (Table 34.4). More recently, the terms *stressed* and *unstressed blood volume* have been introduced to describe the distribution of blood volume between these two compartments. In heart failure, venoconstriction causes a shift of volume into the stressed compartment, which increases both systemic and pulmonary venous congestion and subsequently worsens signs and symptoms of heart failure, especially under conditions of exercise or in response to pharmacologic intervention.^{8,9}

PERCUTANEOUS MECHANICAL CIRCULATORY SUPPORT

The use of surgically implanted left ventricular assist devices (LVADs) as an approach to “bridge” patients to recovery or cardiac transplantation or as “destination therapy” has opened new opportunities for patients with advanced heart failure whose conditions might otherwise have been rendered medically futile. Guidelines for the management of stage D advanced heart failure recommend mechanical circulatory support (Table 34.5).⁷ Nearly 2000 LVADs are implanted annually in the United States alone.⁵ LVADs have evolved from large, bulky, pulsatile systems to smaller, compact, fully implantable continuous-flow (CF) pumps that generate minimally pulsatile blood flow when functioning optimally. These CF-LVADs use rotodynamic

TABLE 34.4 Guidelines for the Use of Pulmonary Artery Catheters in Advanced Heart Failure

Recommendations for invasive evaluation Referenced studies that support the recommendations are summarized in the online data supplements.		
RECOMMENDATIONS	COR	LOE
1. In patients with HF, endomyocardial biopsy may be useful when a specific diagnosis is suspected that would influence therapy (1,2).	2a	B-NR
2. In selected patients with HF with persistent or worsening symptoms, signs, diagnostic parameters and in whom hemodynamics are uncertain, invasive hemodynamic monitoring can be useful to guide management.	2a	C-EO
3. In patients with HF, routine use of invasive hemodynamic monitoring is not recommended (3,4).	3: No benefit	B-R
4. For patients undergoing routine evaluation of HF, endomyocardial biopsy should not be performed because of the risk of complications (5,6).	3: Harm	C-LD

B-NR, LOE B non-randomized; B-R, LOE B randomized; C-EO, LOE C expert opinion; C-LD, LOE C limited data; COR, class of recommendation; HF, heart failure; LOE, level of evidence. Reproduced with permission from Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;79:e263-e421.

TABLE 34.5 Guidelines for the Mechanical Circulatory Support in Heart Failure

Recommendations mechanical circulatory support Referenced studies that support the recommendations are summarized in the online data supplements. ^a		
RECOMMENDATIONS	COR	LOE
1. In select patients with advanced HFrEF with NYHA class IV symptoms who are deemed to be dependent on continuous intravenous inotropes or temporary MCS, durable LVAD implantation is effective to improve functional status, QOL, and survival (1–18).	1	A
2. In select patients with advanced HFrEF who have NYHA class IV symptoms despite GDMT, durable MCS can be beneficial to improve symptoms, improve functional class, and reduce mortality (2,4,7,10,12,17,19).	2a	B-R
3. In patients with advanced HFrEF who have NYHA class IV symptoms despite GDMT, durable MCS devices provide low to intermediate economic value based on current costs and outcomes (20–24).	Value statement: Uncertain value (B-NR)	
4. In patients with advanced HFrEF and hemodynamic compromise and shock, temporary MCS, including percutaneous and extracorporeal ventricular assist devices, are reasonable as a “bridge to recovery” or “bridge to decision” (25–29).	2a	B-NR

^aAlthough optimal patient selection for mechanical circulatory support (MCS) remains an active area of investigation, general indications for referral for MCS therapy include patients with left ventricular ejection fraction below 25% and New York Heart Association (NYHA) Class III–IV functional status despite guideline-directed medical therapy (GDMT), including, when indicated, cardiac resynchronization therapy (CRT), with either high predicted 1- to 2-year mortality rate (e.g., as suggested by markedly reduced peak oxygen consumption and clinical prognostic scores) or dependence on continuous parenteral inotropic support. Patient selection requires a multidisciplinary team of experienced advanced heart failure (HF) and transplantation cardiologists, cardiothoracic surgeons, nurses, and ideally, social workers and palliative care clinicians.

B-NR, LOE B non-randomized; B-R, LOE B randomized; C-LD, LOE C limited data; COR, class of recommendation; GDMT, guideline-directed medical therapy; LOE, level of evidence; HFrEF, heart failure with reduced ejection fraction; LVAD, left ventricular assist device; MCS, mechanical circulatory support; NYHA, New York Heart Association; QOL, quality of life.

Reproduced with permission from Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;79:e263-e421.

pumps to transfer kinetic energy from a circulating impeller to the bloodstream, thereby generating forward flow. CF-LVADs can be divided into two categories: axial-flow and centrifugal-flow pumps. In both cases, blood is pulled into the impeller of the pump via an inlet cannula connected to the LV apex and delivered to the systemic circulation via an outflow cannula connected to either the ascending or descending aorta (Figure 34.5 and Video 34.1).

In parallel to the evolution of surgical LVADs, percutaneously delivered mechanical circulatory support (pMCS) systems have also grown from counterpulsation balloon systems to centrifugally driven circuits or catheter-mounted axial-flow pumps. Both surgical LVADs and pMCS systems are subject to changes in preload and afterload. Inadequate LV preload caused by volume depletion, poor

right ventricular (RV) function, hypotension, pulmonary obstruction, or valvular disease reduces flow generation. Similarly, increased afterload caused by hypertension, elevated systemic vascular resistance, or valvular disease reduces device flow. For these reasons, careful hemodynamic interrogation before, during, and after initiation of pMCS is essential for optimal device function.

The overall goals of pMCS systems are to (1) increase vital organ perfusion, (2) augment coronary perfusion, and (3) reduce ventricular volume and filling pressures, thereby reducing wall stress, stroke work, and myocardial oxygen consumption. Clinical scenarios in which these devices are commonly used include CS, mechanical complications after AMI, high-risk coronary and noncoronary intervention, and for high-risk electrophysiologic ablations. Percutaneous

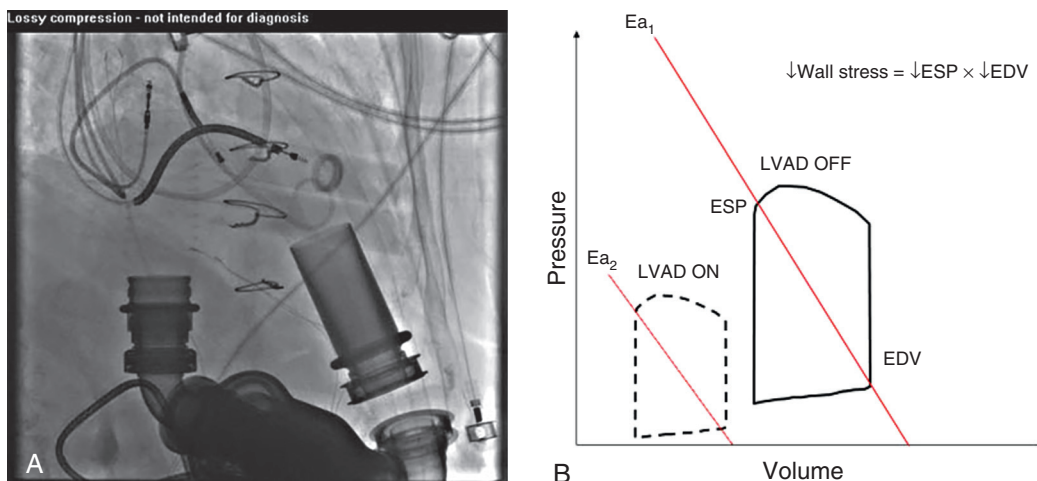


FIGURE 34.5 Hemodynamic profile of continuous-flow left ventricular assist devices (CF-LVAD). **A**, Fluoroscopic image of a HeartMate-II CF-LVAD (Thoratec). **B**, Activation of a continuous flow LVAD reduces left ventricular end-systolic pressure (ESP), end-diastolic pressure, and end-diastolic volume (EDV) with no significant change in arterial elastance (Ea) but a significant reduction in wall stress.

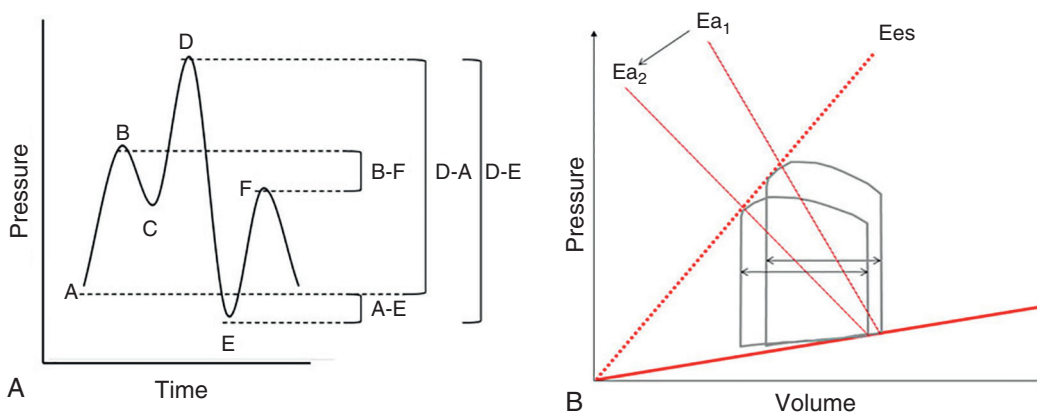


FIGURE 34.6 Hemodynamic profile of intraaortic balloon counterpulsation pumps (IABPs). **A**, IABP tracings acquired at a balloon to a heartbeat synchronization ratio of 1:2 can identify nonaugmented diastolic (A) and systolic (B) pressures, dicrotic-notch pressure (C), augmented diastolic pressure (D), reduced aortic end-diastolic pressure (EDP; E), and augmented or reduced systolic pressure (F). Systolic unloading can be calculated as the difference between nonaugmented and augmented systolic pressures (B–F). Diastolic augmentation is the difference between nonaugmented and augmented diastolic pressures (D–A). Diastolic unloading can be calculated as the difference between nonaugmented diastolic pressure and reduced aortic EDP (A–E). The change in aortic pressure at balloon deflation (deflation pressure) is measured as the difference between augmented diastolic pressure and reduced aortic EDP (D–E). The slope of deflation pressure is measured as the deflation pressure divided by time. **B**, Optimal IABP function reduces left ventricular end-systolic pressure (ESP) and end-diastolic volume (EDV) while increasing stroke volume (SV). Arterial elastance is reduced because of increased SV and reduced ESP. Wall stress is reduced because of decreased ESP and EDV.

circulatory support devices can be categorized by the type of pump used as either pneumatic or continuous blood flow devices. Each device impacts native ventricular function in a unique way and requires adequate preload for optimal use.

Intraaortic Balloon Pump Counterpulsation

The intraaortic balloon counterpulsation pump (IABP) is the most widely used MCS device with more than 4 decades of clinical experience and registry data supporting its use.¹⁰⁻¹⁴ The IABP is a catheter-mounted balloon that augments blood flow by inflating during diastole, which displaces blood volume in the descending aorta and increases mean aortic pressure, thereby potentially augmenting coronary perfusion. Upon deflation, during systole, the

IABP generates a pressure sink, which is filled by ejecting blood from the heart. Optimal IABP function should increase diastolic aortic pressure, reduce aortic and LV systolic pressure, increase systemic MAP, reduce LV diastolic volume and pressure, and increase coronary perfusion pressure. The hemodynamic effect of an IABP can be directly measured using tracings obtained from the IABP console to determine the magnitude of systolic unloading and diastolic augmentation (Figure 34.6).

The pioneering work of Kantrowitz, “Webe,” Janicki, Sarnoff, Schreuder, Kern, and many others has established that the hemodynamic impact of balloon counterpulsation is primarily determined by four factors: (1) the magnitude of diastolic pressure augmentation, (2) the magnitude of reduced systolic pressure, (3) the magnitude of volume displacement, and (4) the timing of balloon inflation and

deflation.¹³⁻²⁰ IABP balloon capacity ranges from 34 to 50 cc. Larger capacity IABPs potentially offer better hemodynamic support than standard 40 cc IABPs.²¹ In addition to balloon capacity, the hemodynamic effects of IABP are determined by frequency and timing of IABP inflation and deflation, its position in the descending aorta, shape, and occlusivity, as well as biologic factors, including heart rate, blood pressure, and aortic compliance.²²⁻²⁵

The advantages of IABP include its relative cost compared with other assist devices, ease of insertion, and widespread familiarity with its insertion technique. However, its use in the setting of CS is likely best when deployed early in the management of CS and decompensated heart failure. Major complications, including acute limb ischemia, severe bleeding, IABP failure or leak, or death directly related to IABP insertion, occurred at a frequency of 2.6% in 16,909 patient case records in the Benchmark Registry.²⁶ Clinician expertise, sheathless insertion, and smaller IABPs are associated with decreased incidences of vascular complications.^{27,28}

Percutaneous Rotodynamic Pumps

Both the Impella (Abiomed) and TandemHeart (CardiacAssist) devices are rotodynamic pumps that generate continuous, minimally pulsatile blood flow when functioning optimally. The Impella devices are catheter-mounted axial-flow pumps with an intracorporeal motor and short drive-line that are placed into the left ventricle in retrograde fashion across the aortic valve. The pump transfers kinetic energy from a circulating impeller to the bloodstream, which results in continuous blood flow from the left ventricle to ascending aorta. The Impella 2.5 LP and CP devices can be deployed without the need for surgery, and the Impella 5.0 and Impella 5.5 devices require surgical vascular access (Figure 34.7 and Videos 34.2 and 34.3). At present, the CP device is the most commonly implanted

Impella pump followed by rapidly growing experience with the Impella 5.5 pump in the United States. In contrast, the TandemHeart device is an extracorporeal centrifugal flow pump that reduces LV preload by transferring oxygenated blood from the left atrium to the descending aorta via two cannulas: a transseptal inflow cannula in the left atrium and an arterial outflow cannula in the femoral artery. The net effect of these devices is to reduce native LV volume and pressure while increasing MAP without greatly influencing ventricular afterload (Figure 34.8 and Videos 34.4 and 34.5). An advantage of the Impella 2.5 and CP devices is their ease of insertion via a single arterial access, and an advantage of the TandemHeart device is the magnitude of support provided without the need for surgical vascular access (Table 34.6). No large prospective studies comparing these CF devices head-to-head exist.

Other centrifugal pumps include the Centrimag (Thoratec), Rotaflow (Maquet Getinge Group), and Biomedicus (Medtronic) pumps, which are more commonly implanted surgically or used to provide flow for venoarterial extracorporeal membrane oxygenation (VA-ECMO). Over the past decade, VA-ECMO use for AMI has grown by 11-fold in the United States and Europe,^{29,30} driven in part by growing experience with percutaneous cannulation; the need for cardiorespiratory support during the COVID-19 pandemic; and increasing collaboration between cardiac surgery, interventional cardiology, and advanced heart failure specialists. VA-ECMO is more commonly used to enhance systemic oxygenation during cardiorespiratory collapse or biventricular failure. VA-ECMO displaces blood volume from the venous to arterial circulation. As a result, reduced right and LV volumes can be observed with a concomitant increase in MAP and both LV systolic and diastolic pressures. Not all patients develop increased ventricular load while on VA-ECMO. Patients with low MAP, low LVEF, and high cardiac filling pressures are predisposed to develop LV distention after initiation of VA-ECMO.

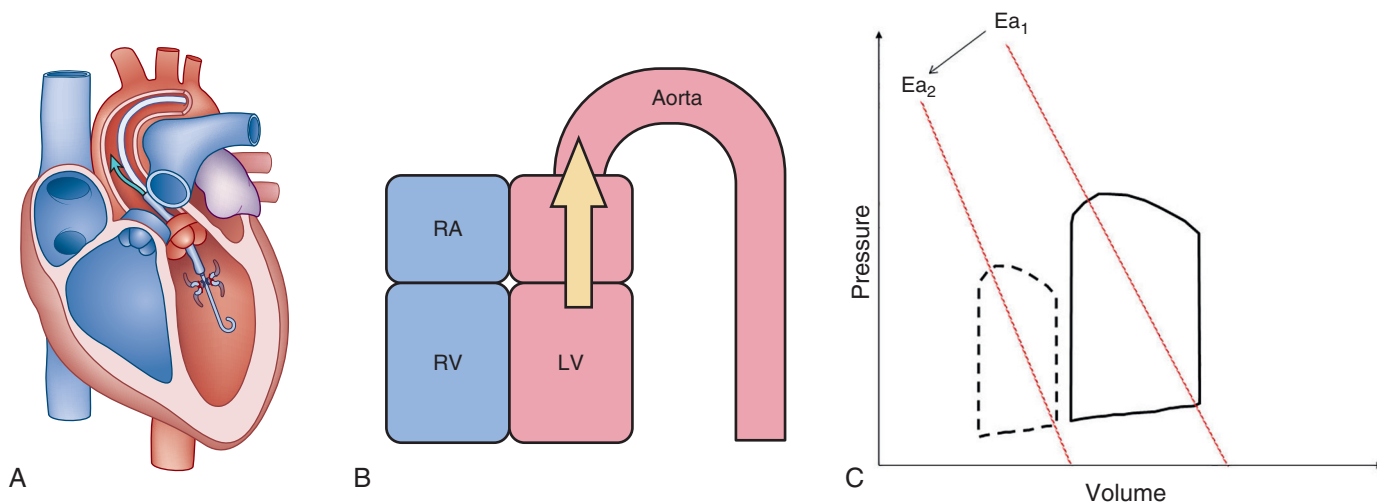


FIGURE 34.7 Hemodynamic profile of the Impella pump. **A** and **B**, The Impella pump is an intracorporeal axial-flow catheter deployed into the arterial circulation via either percutaneous or surgical access. The pump rests across the aortic valve and withdraws blood from the left ventricle (LV) into the ascending aorta. **C**, Optimal Impella pump function reduces left ventricular end-systolic pressure (ESP) and end-diastolic volume (EDV) while decreasing native left ventricular stroke volume (SV) by directly displacing blood from the left ventricle. Arterial elastance (E_a) is slightly increased because of reduced SV; however, left ventricular afterload or wall stress is reduced because of decreased ESP and EDV. RA, Right atrium; RV, right ventricle.

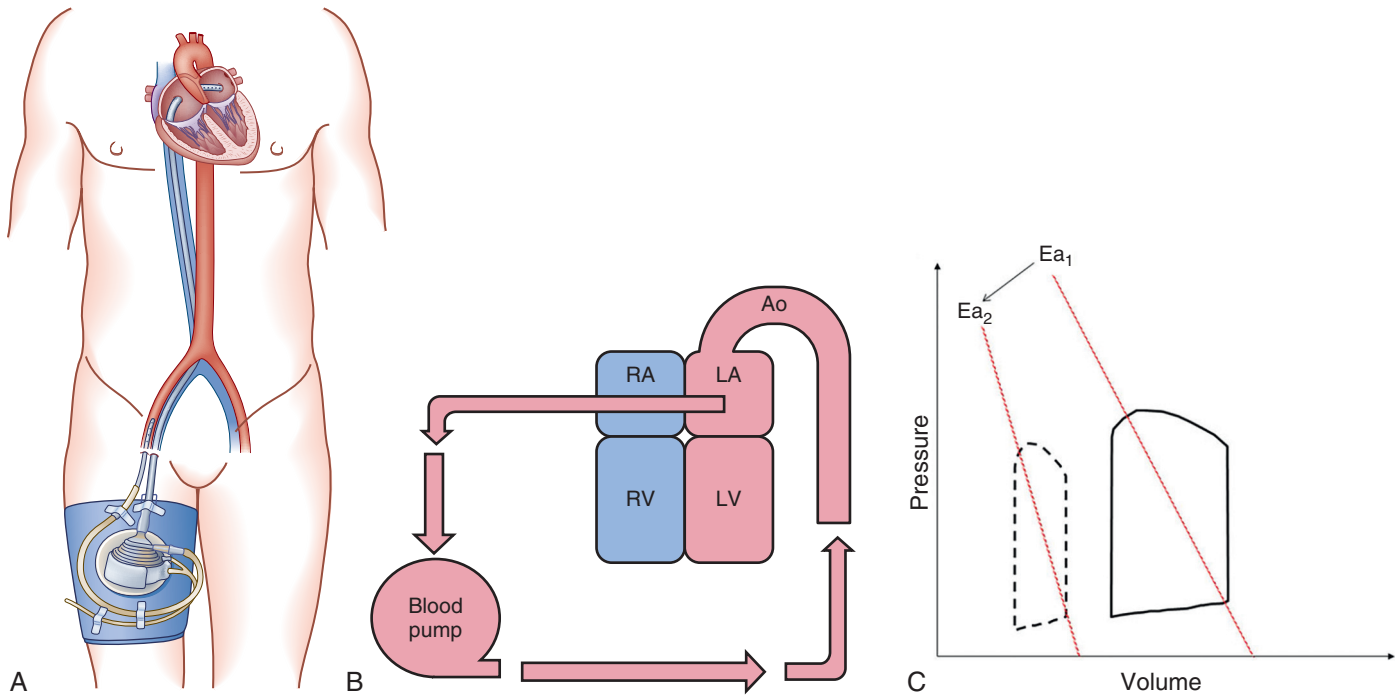


FIGURE 34.8 Hemodynamic profile of the TandemHeart pump. **A** and **B**, The TandemHeart pump is an extracorporeal, centrifugal-flow pump that delivers oxygenated blood from the left atrium via a transseptal inflow cannula into the systemic circulation via a femoral arterial outflow cannula. **C**, Optimal TandemHeart pump function reduces left ventricular end-systolic pressure (ESP) and end-diastolic volume (EDV) while decreasing native left ventricular stroke volume (SV) by reducing left ventricular preload. Arterial elastance (Ea) is slightly increased because of reduced SV; however, left ventricular afterload or wall stress is reduced because of decreased ESP and EDV. Ao, Aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

TABLE 34.6 Advantages and Disadvantages of Percutaneous Mechanical Circulatory Support Devices

PERCUTANEOUS ASSIST DEVICE	ADVANTAGES	DISADVANTAGES
IABP	- Ease of insertion - Widespread familiarity with insertion technique - Relative low cost compared with other devices - Bedside placement is feasible - Improves coronary perfusion - Anticoagulation is recommended but not required	- Moderate hemodynamic support in moderate to severe cardiogenic shock - Contraindicated in severe aortic insufficiency
Impella devices	- Provide ≤ 3.5 L/min of flow (surgical 5.0 implant provides 5.0 L/min) - Ease of insertion - Improve coronary perfusion	- Require fluoroscopy for placement - Impella 5.0 requires surgical cutdown for placement - Require systemic anticoagulation - Contraindicated in mechanical aortic valves or severe AS - Contraindicated in patients with LV thrombus
TandemHeart	- Provides 5.0 L/min of flow - Can be used to support left right ventricles (or both) - Can be used in severe aortic insufficiency - No surgical cutdown necessary for placement - Improves coronary perfusion	- Requires fluoroscopy for placement - Transseptal puncture for LV support - Requires systemic anticoagulation
VA-ECMO	- Ease of insertion - Does not require fluoroscopy for placement - Offers complete cardiopulmonary support	- Requires systemic anticoagulation - Acute increase in LV afterload, necessitating venting of the LV - Requires a perfusionist at the bedside - Does not improve coronary perfusion

AS, aortic stenosis; IABP, intraaortic balloon pump; LV, left ventricular; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

▶ This increase in LV afterload or wall stress occurs in contrast to the Impella or TandemHeart devices because there is no direct venting of the left ventricle with VA-ECMO (Figure 34.9 and Video 34.6). For this reason, operators have combined VA-ECMO with an IABP, Impella

device, or a transseptal left atrial (LA) single- or multi-stage cannula to negate the effect of increased LV afterload during VA-ECMO support (Figure 34.10). Observational data suggest that the combination of VA-ECMO plus a venting strategy may reduce in-hospital mortality rates

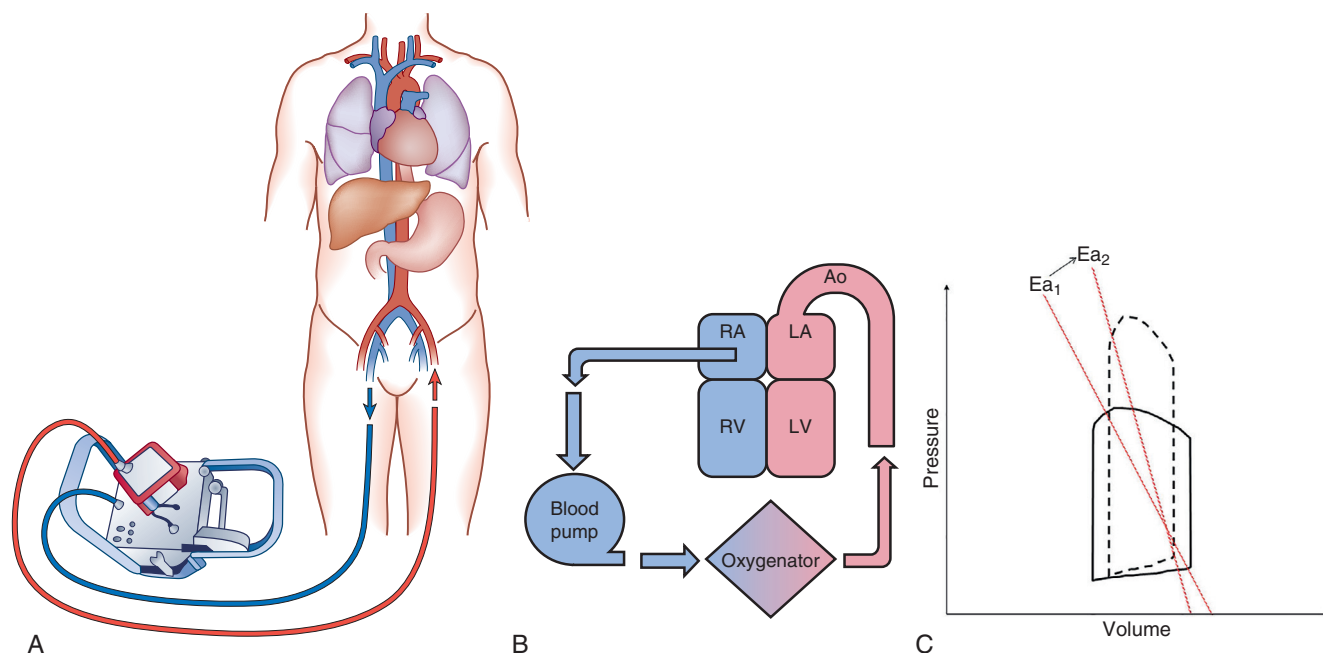


FIGURE 34.9 Hemodynamic profile of venoarterial extracorporeal membrane oxygenation (VA-ECMO). **A** and **B**, VA-ECMO is an extracorporeal, centrifugal-flow pump that delivers deoxygenated blood from the venous system via an inflow cannula through an oxygenator and into the systemic circulation via a femoral arterial outflow cannula. **C**, Optimal VA-ECMO pump function reduces left ventricular stroke volume and increases end-systolic pressure (ESP) and end-diastolic pressure (EDP). Arterial elastance (E_a) and LV afterload or wall stress are significantly increased because of increased ESP. Ao, Aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

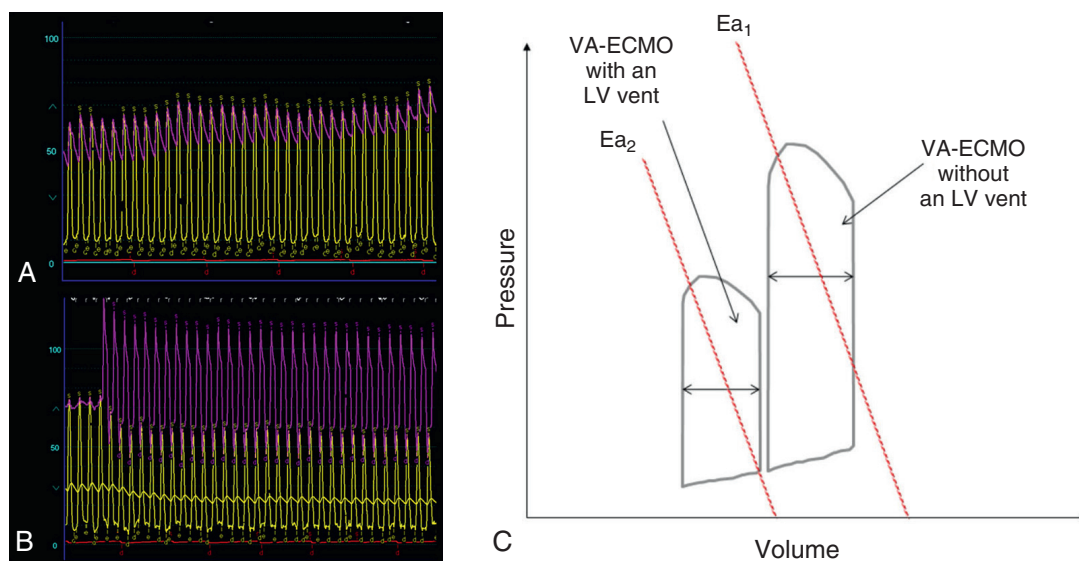


FIGURE 34.10 Hemodynamic profile of venoarterial extracorporeal membrane oxygenation with and without left ventricular (LV) venting. **A**, A double-lumen pigtail catheter during activation of venoarterial extracorporeal membrane oxygenation (VA-ECMO) shows increased LV systolic pressure and reduced aortic pulse pressure. **B**, Initiation of an intraaortic balloon pump (IABP) with VA-ECMO shows reduced LV systolic pressure (venting) and elevated aortic diastolic pressure. **C**, Venting of the left ventricle with an IABP, Impella device, or transseptal left atrial cannula during VA-ECMO support reduces LV end-systolic pressure and end-diastolic volume. E_a , Arterial elastance.

among patients with CS requiring VA-ECMO.³¹ Algorithms for use of LV mechanical unloading with VA-ECMO are currently in development. Advantages of VA-ECMO include the relative ease of insertion, the ability to support systemic oxygenation or biventricular failure, and the ability to provide cardiopulmonary support during ventricular tachycardia or fibrillation (Table 34.7).

CIRCULATORY SUPPORT FOR CARDIOGENIC SHOCK AND ADVANCED HEART FAILURE

Cardiogenic shock is a major cause of global morbidity and mortality in patients diagnosed with AMI or heart failure. Shock from any cause is characterized by tissue hypoperfusion, leading to end-organ damage. CS is defined as

TABLE 34.7 Hemodynamic Effects of Percutaneous Mechanical Circulatory Support Devices

	ESP	EDV	WALL STRESS	STROKE WORK	MAP	EDP
IABP	↓	↓	↓	↓	↑	↓
Impella 5.0	↓↓	↓	↓↓	↓↓	↑↑	↓
TandemHeart	↓	↓↓	↓↓	↓↓	↑↑	↓↓
VA-ECMO	↑↑	←	↑	↑	↑↑	↓

EDP, End-diastolic pressure; EDV, end-diastolic volume; ESP, end-systolic pressure; IABP, intraaortic balloon pump; MAP, mean arterial pressure; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

TABLE 34.8 Guidelines for the Management of Cardiogenic Shock

Recommendations for evaluation and management of cardiogenic shock Referenced studies that support the recommendations are summarized in the online data supplements.		
RECOMMENDATIONS	COR	LOE
1. In patients with cardiogenic shock, intravenous inotropic support should be used to maintain systemic perfusion and preserve end-organ performance (1–8).	1	B-NR
2. In patients with cardiogenic shock, temporary MCS is reasonable when end-organ function cannot be maintained by pharmacologic means to support cardiac function (9–17).	2a	B-NR
3. In patients with cardiogenic shock, management by a multidisciplinary team experienced in shock is reasonable (17–22).	2a	B-NR
4. In patients presenting with cardiogenic shock, placement of a PA line may be considered to define hemodynamic subsets and appropriate management strategies (23–27).	2b	B-NR
5. For patients who are not rapidly responding to initial shock measures, triage to centers that can provide temporary MCS may be considered to optimize management (17–22).	2b	C-LD

B-NR, LOE B non-randomized; C-LD, LOE C limited data; COR, class of recommendation; LOE, level of evidence; MCS, mechanical circulatory support; PA, pulmonary artery. Reproduced with permission from Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:e263-e421.

tissue hypoperfusion secondary to cardiac failure despite adequate circulatory volume and LV filling pressure. Specifically, hemodynamic criteria for CS include a systolic blood pressure less than 90 mm Hg for more than 30 minutes or a decrease in mean arterial blood pressure greater than 30 mm Hg below baseline with a cardiac index (CI) of less than 1.8 L/min (m²) without hemodynamic support or less than 2.2 L/min (m²) with support and a pulmonary capillary wedge pressure (PCWP) greater than 15 mm Hg.³² The incidence of CS after AMI has remained relatively stable over the past 30 years and ranges between 7% and 9%.^{33,34} A recent evaluation of the National Registry of Myocardial Infarction (NRM) reported that CS occurred in 8.6% of patients presenting with AMI, defined as ST-segment elevation or new left bundle branch block, between June 1995 and May 2004. In this study, only 29% of patients presented with CS upon presentation, and 71% developed CS after admission.³³ In the landmark SHOCK (Should we emergently revascularize Occluded Coronary arteries for cardiogenic shock?) trial, registry time from onset of AMI to CS was 7 hours.³⁵ In the TRACE (Trandolapril Cardiac Evaluation) registry, early development of CS within 48 hours of admission was associated with significantly lower 30-day mortality rate than in patients with late development of CS.³⁶

Guidelines for management of CS focus on pharmacologic and mechanical circulatory support (Table 34.8). Mortality rates associated with CS are high. In the SHOCK trial registry, the in-hospital mortality rate was 60%. This finding was consistent with reported in-hospital mortality rates from the NRM, which ranged from 60.3% in 1995 to 47.9% in 2004.^{33,35} Importantly, CS can develop in both ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI). The GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries)-IIb trial reported CS in 4.2% of patients with STEMI and 2.5% of patients with NSTEMI. The mean time to onset of CS after STEMI was 9.6 hours compared with 76.3 hours after NSTEMI. Despite variable times to onset, the in-hospital mortality rate was not significantly different between the two groups.³⁷

Several historic classification schemes for CS after an AMI exist, including the Killip and Forrester classes. Killip classes were first defined in 1967 in an observational series of 250 patients presenting with an AMI and without cardiac arrest. Killip class IV defines CS and was associated with a 67% 30-day mortality rate.³⁸ In 1977, Forrester and colleagues³⁹ expanded the Killip definitions to include hemodynamic parameters such as PCWP and CI. Given the advances in treatment for AMI and the increasing number of patients

with heart failure, more commonly applied classification systems for the use of MCS include the NYHA class and INTERMACS class.⁵ No predictive tools or classification schemes to identify candidates for percutaneous MCS in advanced heart failure or CS exist. The Society for Coronary Angiography and Intervention (SCAI) recently developed a staging system to define shock severity that ranges from SCAI stage A (at risk) to E (extremis). The SCAI Shock Staging system is directly associated with increasing in-hospital mortality rates and has been refined to increase practical application for use in clinical practice.^{40,41}

Clinical trials examining the use of percutaneous circulatory support devices have failed to identify reduced in-hospital mortality rates in high risk percutaneous coronary intervention (PCI) or CS. No large randomized studies examining the utility of any percutaneous MCS device in advanced heart failure exist. Registry data have historically supported the use of IABPs^{11,42,43}; however, recent studies attempting to identify optimal candidates for IABP support in high-risk PCI, acute MI, or CS have shown no significant benefit associated with elective IABP insertion. The CRISP-AMI (Counterpulsation Reduces Infarct Size Acute Myocardial Infarction) trial showed that IABP implantation immediately before revascularization for an anterior STEMI does not reduce infarct size or improve short-term survival.⁴⁴ The IABP-SHOCK II study suggested that not all patients presenting with an ACS with marginal blood pressures and clinical evidence of hypoperfusion benefit from IABP activation.⁴⁵ A prospective, multi-center, randomized controlled trial of the IMPELLA RECOVER LP 2.5 System Versus intra aortic balloon pump (IABP) in patients undergoing non emergent high risk PCI (PROTECT II) showed no difference in major adverse cardiovascular events (MACEs) between IABP and the Impella 2.5 axial-flow catheter.⁴⁶ The BCIS (Balloon Pump Assisted Coronary Intervention Study)-1 also showed no reduction in short-term mortality with IABP insertion before high-risk PCI; however, follow-up data suggested a possible long-term benefit up to 5 years after PCI.^{47,48}

For the Impella device, the recently published PROTECT II study was terminated early because of a determination of futility. No difference in MACEs was observed between IABP and Impella 2.5 for patients undergoing high-risk PCI.⁴⁵ Subsequent analysis of the PROTECT II study has generated potentially important insight into the timing of device activation for high-risk PCI and the potential benefits of multivessel revascularization with concomitant MCS. Further studies are required to confirm these observations. Furthermore, a meta-analysis of smaller studies evaluating these devices for CS showed improved hemodynamic profiles associated with the Impella and TandemHeart devices compared with IABP, however, showed no impact on short-term mortality.⁴⁹ The use of VA-ECMO in prolonged cardiac arrest with reversible disease and severe CS has shown promising results in several observational studies and small case series, with survival rates ranging from 20% to 40%.⁵⁰⁻⁵⁴ Several large randomized clinical trials are actively testing the utility of pMCS. Based on extensive preclinical data and a pilot study, the STEMI-Door to Unload (DTU) Trial is testing whether LV unloading plus delayed reperfusion reduces

myocardial infarct size and subsequent heart failure among patients with anterior STEMI compared with primary reperfusion alone.⁵⁵⁻⁵⁷ The PROTECT IV trial is testing whether preemptive support with an Impella CP pump improves survival compared with no pMCS or IABP support among patients with low LVEF undergoing complex PCI. The extracorporeal life support (ECLS) Shock trial is testing whether early initiation of VA-ECMO improves survival among patients with AMI and CS compared with non-VA-ECMO support strategies.⁵⁸ The Danish-German (DanGer) Shock Trial is testing whether Impella support reduces the 180-day mortality rate compared with non-Impella support strategies in patients with AMI and CS.⁵⁹ Early Impella Support in patients with ST-segment elevation myocardial infarction complicated by cardiogenic shock: The RECOVER IV trial is testing whether a management strategy using Impella support before PCI improves survival compared with non-Impella-based support strategies among patients with STEMI and CS.

INTERVENTIONAL THERAPY FOR RIGHT HEART FAILURE

Although most clinical and preclinical science has focused on LV failure, the importance of RV function has become more apparent over the past few decades. Causes of RV failure can be broadly categorized into three groups: (1) direct RV myocyte injury in the setting of MI, myocarditis, or after cardiac surgery; (2) volume overload secondary to right-sided valvular insufficiency or after placement of an LVAD; and (3) pressure overload caused by pulmonary hypertension, pulmonic valve stenosis, or a pulmonary embolus. Irrespective of the mechanism, the presence of RV dysfunction is a primary determinant of functional capacity and prognosis.

Several studies have examined the clinical importance of RV failure in the setting of an AMI. RV dysfunction as defined by echocardiography can be identified in up to 50% of patients presenting with an acute inferior wall myocardial infarction (IWMI).⁶⁰⁻⁶² Of these patients, 15% to 25% exhibit hemodynamic instability suggestive of RV involvement, yet histologic infarction of the RV free wall occurs in only 3% to 5% of patients with an acute IWMI.⁶³ In a substudy of the SHOCK trial, RV-dominant CS was associated with similar in-hospital mortality rates as LV-dominant CS (53.1% vs 60.8%; $P = .3$) despite a younger age, lower rate of anterior MI, and higher likelihood of single-vessel disease among RV-dominant shock patients.⁶⁴ Furthermore, a meta-analysis of several studies showed significantly higher in-hospital mortality rate and higher incidence of shock, ventricular arrhythmias, and advanced atrioventricular block if AMI involved the RV.⁶⁵

Acute RV failure can occur in the setting of ischemia caused by either a coronary occlusion or after open heart surgery and can occur after direct myocyte injury secondary to myocarditis (Figure 34.11). In these settings, RV failure is characterized by both RV systolic and biventricular diastolic failure. More commonly after acute proximal right coronary artery (RCA) occlusion, both RV free-wall and interventricular septal ischemia reduce RV cardiac output and a subsequent reduction in LV preload.⁶⁶ RV

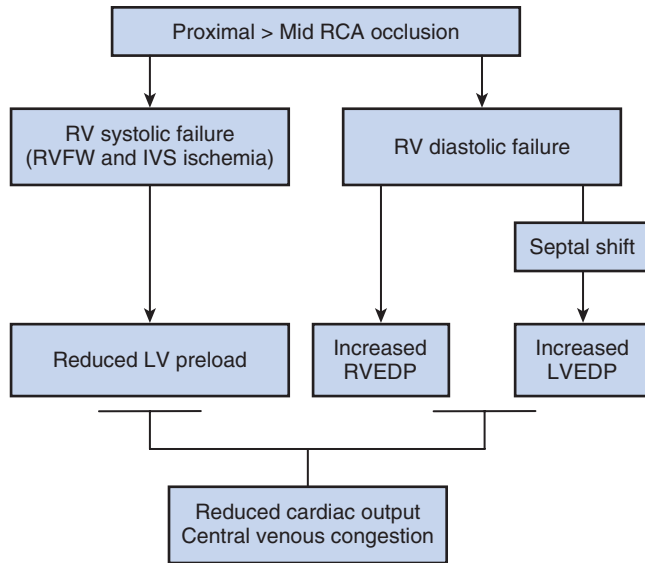


FIGURE 34.11 Pathophysiology of right ventricular (RV) myocardial infarction. *IVS*, interventricular septum; *LV*, left ventricular; *LVEDP*, left ventricular end-diastolic pressure; *RCA*, right coronary artery; *RVEDP*, right ventricular end-diastolic pressure; *RVFW*, right ventricular free wall.

ischemia also impairs RV diastolic function, which in combination with RV systolic failure causes RV pressure and volume overload with subsequent RV dilatation.⁶⁷ After LVAD implantation, increased venous return to the RV can cause volume overload and lead to RV dilatation.⁶⁸ In the setting of primary or secondary pulmonary hypertension, increased RV afterload leads to RV hypertrophy and fibrosis, which ultimately contributes to adverse cardiac remodeling and progressive RV failure. Irrespective of the primary cause of RV failure, in the presence of an intact pericardium, RV dilation compresses the LV cavity, thereby equalizing biventricular diastolic filling pressures. The combination of RV systolic and biventricular diastolic dysfunction reduces systemic cardiac output, worsens renal and hepatic congestion, and impairs global coronary blood flow.

Contemporary management of RV failure includes reversal of the primary cause, volume resuscitation, inotropic support, and pulmonary vasodilation, which serve to maintain RV preload, enhance RV contractility, and reduce RV afterload, respectively.⁶⁹ In refractory RV failure, treatment options are limited to surgical right ventricular assist devices (RVADs), VA-ECMO, atrial septostomy, and cardiac transplantation. Percutaneously delivered circulatory support for RV failure is an emerging field with several investigational options, including the IABP, the TandemHeart centrifugal flow pump, and the axial-flow Impella RP catheter.⁷⁰ Appropriate patient-device selection, timing of device use, weaning parameters, and the hemodynamic impact of each device remain poorly understood and represent a new era in percutaneous therapies for patients with advanced heart failure.

Over the past 3 decades, mechanical support devices for right heart failure have passed through several generations of development. First-generation, surgically implanted RV pumps were pulsatile with valves located within the inflow and outflow segments.⁷¹ Early attempts

at dedicated RV support devices include pulmonary artery balloon counterpulsation to reduce RV afterload, which required surgical implantation and thus had limited clinical application.⁷² By the early 1990s, CF RVADs demonstrated better hemodynamic support and clinical outcomes than pulsatile devices for RVF.⁷³ Second- and third-generation surgical devices now include rotodynamic pumps that transfer rotational kinetic energy to the bloodstream and involve either multiple moving parts (impeller and bearings) or a single moving part (impeller), respectively.⁷¹

Percutaneously delivered assist devices that specifically address RV failure are relatively new. Historically, percutaneous mechanical support for RVF has been limited to the IABP. Nordhaug and colleagues⁷⁴ performed one of the few preclinical studies examining the impact of IABP use in a model of acute RV failure caused by microembolization of the RCA. In this study, IABP activation caused a small but statistically significant increase in systemic MAP, total cardiac output, and biventricular stroke volume while reducing both LV and RV afterload. Furthermore, a trend toward increased RCA flow was observed with IABP application. These data support the use of IABPs in the setting of acute RVMI; however, the hemodynamic impact is small and does not provide optimal RV unloading.⁷⁴

In 2006, the first successful implantation of a percutaneously delivered RVAD in the setting of RV failure after AMI⁷⁵ using the TandemHeart centrifugal flow pump was reported (Figure 34.12). Since then, the TandemHeart right ventricular assist device (TH-RVAD) has been implanted for RV failure in the setting of AMI,⁷⁶ post-LVAD implantation,⁷⁷ severe pulmonary hypertension,⁷⁸ and cardiac rejection after orthotopic heart transplantation.⁷⁹ As a centrifugal pump that generates CF with a minimal, low-amplitude pulsatile component, the TH-RVAD may more closely approximate native RV function and may have hemodynamic benefits over more commonly used surgically placed pulsatile RVADs. Furthermore, percutaneous application of a mechanical circulatory support device provides the opportunity for early intervention in the cascade of refractory RV failure without the need for surgery.

Another mechanical option for acute RV failure is VA-ECMO, which enhances systemic oxygenation during cardiorespiratory collapse and reduces RV stroke work while maintaining adequate mean pulmonary pressures and LV preload. VA-ECMO is particularly beneficial in cases of biventricular failure or refractory ventricular arrhythmias.

More recently, the Impella RP (Abiomed) axial-flow catheter was developed and is currently undergoing evaluation as a support option for patients with RV failure.⁸⁰ Whether axial- or centrifugal-flow pumps provide better support for RV failure remains unknown. The Recover Right Study is currently underway to examine the safety and feasibility of the Impella RP catheter. Whereas one potential advantage of centrifugal-flow pumps is the ability to splice an oxygenator into the circuit and thereby provide ECMO support while unloading the RV, an advantage of the Impella RP may be the ability to deploy the device using a single venous access site.

At present, minimal data exploring the clinical utility of percutaneous RV support devices exist. Several studies

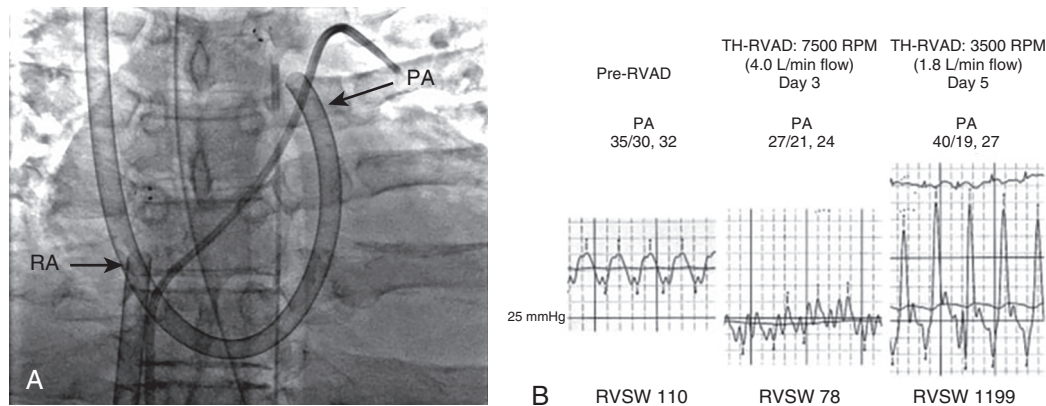


FIGURE 34.12 Hemodynamic profile of the TandemHeart pump as a right ventricular support device (TH-RVAD). **A**, The TandemHeart pump is an extracorporeal, centrifugal-flow pump that delivers blood from the right atrium (RA) into the pulmonary artery (PA), thereby bypassing the right ventricle (RV). **B**, Pulmonary artery (PA) tracings show a narrow pulse pressure and low RV stroke work (RVSW) before RVAD implantation. During TH-RVAD support, the PA pulse pressure narrows, and both mean PA pressure and RVSW are reduced. After recovery of the RV, the TH-RVAD is weaned to a low flow setting, which reveals improved PA pulse pressure and RVSW.

have shown the potential benefits of centrifugal-flow pumps in RV failure using surgical and hybridized surgical-percutaneous deployment with the Centrimag (Thoratec)⁸¹ and the Rotaflow (Maquet Getinge Group)⁸² pumps, respectively. Novel dual-lumen cannulas, including the ProtekDuo (LivaNova), have also been introduced into clinical practice to provide right atrium-to-pulmonary artery (PA) bypass using a single venous access site. A single-center experience with fully percutaneous deployment of the TH-RVAD in nine patients with medically refractory RV failure identified that compared with preprocedural values, MAP (57 ± 7 vs 75 ± 19 mmHg; $P < .05$), right atrial pressure (22 ± 3 vs 15 ± 6 mmHg; $P < .05$), cardiac index (1.5 ± 0.4 vs 2.3 ± 0.5 L/min/m²; $P < .05$), mixed venous oxygen saturation (40 ± 14 vs 58 ± 4 %; $P < .05$), and RV stroke work (3.4 ± 3.9 vs 9.7 ± 6.8 g/m/beat; $P < .05$) improved significantly within 24 hours of TH-RVSD implantation. The in-hospital mortality among nine patients was 44% ($n = 4$). Time from admission to TH-RVSD placement was lower in subjects who survived to hospital discharge (0.9 ± 0.8 vs 4.8 ± 3.5 days; $P = .04$, survivors vs nonsurvivors). In this report, no mechanical complications were observed during or after device implantation, suggesting that TH-RVSD is clinically feasible and may not be associated with excess risk.⁸³

The THRIVE (TandemHeart in Right Ventricular support) study was a retrospective, observational registry of 46 patients receiving a TH-RVAD for RV failure in eight tertiary care centers in the United States. The central finding of this report was that implantation of the TH-RVAD is clinically feasible via both surgical and percutaneous routes and is associated with acute hemodynamic improvement in RV failure across a broad variety of clinical presentations. This study also identified that evaluation of RV failure in real-world practice did not always involve quantitative measures of RV function and further does not always include comprehensive evaluation and management of concomitant LV dysfunction. In the in-hospital mortality rate varied widely among different indications for mechanical RV support and was lowest among patients with RV failure in the setting of AMI or after LVAD implantation. Increased age, biventricular failure, and

TIMI (Thrombolysis in Myocardial Infarction) major bleeding were more commonly observed in patients not surviving to hospital discharge.⁸⁴

Because the TH-RVSD provides centrifugal flow from the RA to main PA, penetration of cannulas into the heart is required to bypass a poorly functioning RV. Close monitoring for evidence of cannula migration is essential and can be prevented by marking cannula depths at the skin incision site, minimizing patient mobility, and stabilizing cannulas during patient transport. Echocardiography and daily chest radiographs to confirm cannula position also reduce the likelihood of cannula migration. Antegrade migration into a secondary branch of the PAs could present as hypoxic respiratory failure, hemothorax, hemoptysis, decreased cardiac output, and an acute decrease in TH-RVAD flows. Retrograde migration into the right ventricle may result in decreased cardiac output caused by tricuspid regurgitation (TR), reduced TH-RVAD flows, or ventricular arrhythmia. Although antegrade or retrograde cannula migration are possible, no institutions in the THRIVE study reported migration as a device-associated complication.⁸⁴ TIMI major bleeding was the most common complication associated with the TH-RVSD and is likely to be secondary to the need for continuous anticoagulation and sheathless deployment of the device cannulas. Bleeding is best controlled by close monitoring of anticoagulation and minimizing patient movement while on support. Mechanical complications associated with the TH-RVSD were rare and included isolated cases of injury to the main PA during surgical deployment only and an isolated case of retroperitoneal bleed associated with peripheral venous cannulation. The development of deep vein thrombosis was reported in three cases despite required anticoagulation during device support and may be caused by severe multiorgan dysfunction or partial obstruction of venous flow by cannulas in the inferior vena cava (IVC).

With the introduction of RV support options, the field of percutaneous mechanical circulatory support represents an important approach to the management of advanced heart failure and provides an opportunity to rapidly deliver

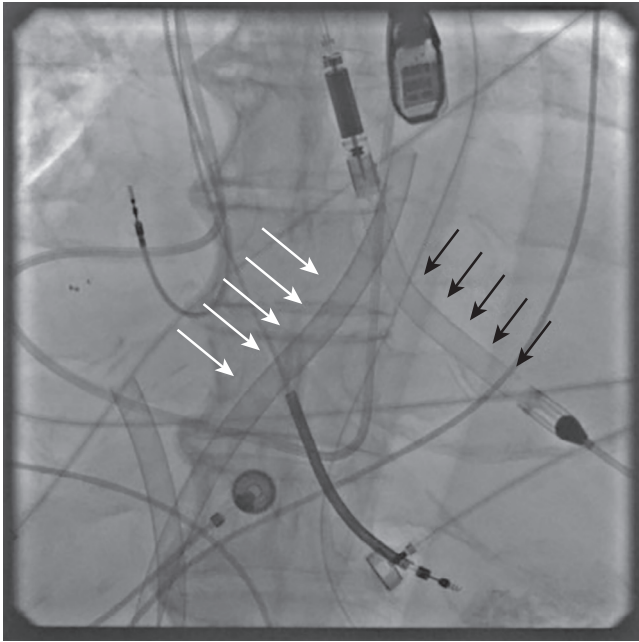


FIGURE 34.13 Percutaneous biventricular circulatory support. Fluoroscopic image showing an Impella 5.0 left ventricular assist device (VAD) implanted via the axillary artery across the aortic valve (*black arrows*) and a Tandem-Heart VAD implanted for simultaneous right ventricular support with an inflow cannula positioned in the inferior vena cava-right atrium junction and an outflow cannula in the main pulmonary artery (*white arrows*).

univentricular or biventricular (Figure 34.13) mechanical support as either a bridge to definitive therapy or recovery as advances in coronary intervention, cardiac surgery, pulmonary hypertension, transplant medicine, and VAD technology provide more options for patients surviving CS.

Emerging Percutaneous Circulatory Support Devices

Innovation in device therapy for advanced heart failure continues to push the envelope. Emerging devices for acute circulatory support include the Percutaneous Heart Pump (Thoratec), which is a catheter-mounted, self-expanding axial-flow pump with a driveline and extracorporeal motor that can conceptually generate up to 4.5 L/min of flow through a 13-Fr arterial access site (Figure 34.14). Development of this technology was discontinued after issues with fluid ingress into the external motor limited device function in the acute setting.⁸⁵ Several self-expanding transvalvular pumps in the same class are in development. Several novel percutaneous circulatory support devices are in development.^{86,87} The iVAC2L is another percutaneously delivered transvalvular pump technology that uses an external pneumatically driven bladder pump that withdraws blood from the left ventricle and ejects blood into the ascending aorta. The pump is

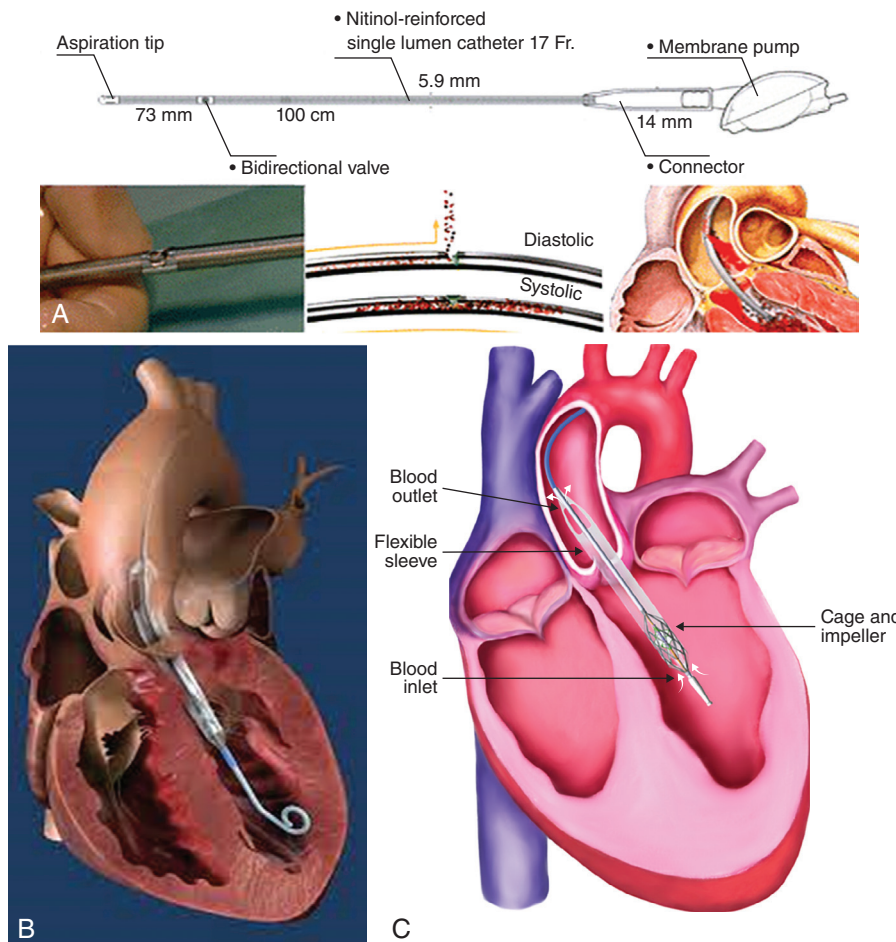


FIGURE 34.14 Emerging percutaneous circulatory support devices. **A**, The iVAC 2L transvalvular extracorporeal pneumatic pump. **B** and **C**, The Impella Expandable CP and Magenta Elevate System transvalvular pumps with self-expanding cannulas and intracavitary impellers in the left ventricle.

designed to increased cardiac output and systemic perfusion and has been used for high-risk coronary intervention.⁸⁷ The Impella Expandable CP (ECP) is novel technology currently being tested for safety and feasibility. The ECP is currently the smallest caliber transvalvular pump requiring only a 9-Fr sheath for delivery. The technology uses an extracorporeal motor connected to an impeller positioned inside the left ventricle via a driveline. The impeller displaces blood from the left ventricle into the aorta via a collapsible cannula. The Magenta Elevate System is another transvalvular pump using a self-expanding cannula and intraventricular impeller tethered to an extracorporeal motor. These devices recently completed first-in-human studies and are under investigation.

PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH HEART FAILURE

Ischemic cardiomyopathy is the most common cause of HFrEF in developed countries. The introduction of myocardial viability assessment over the past 2 decades has advanced our ability to identify patients who would potentially benefit from coronary revascularization. Observational studies estimate the prevalence of myocardial viability in patients with reduced LVEF to be as high as 50% of patients, depending on the assessment modality chosen.^{88,89} Several studies published before the STICH (Surgical Treatment for Ischemic Heart Failure) trial reported improved symptoms, functional class, and reduced mortality rate after revascularization of viable myocardium.⁹⁰⁻⁹³ A meta-analysis of non-randomized studies including more than 3000 patients with a mean LVEF of 32% ($\pm 8\%$) demonstrated a 79.6% reduction in annual mortality rate (16% vs 3.2%; chi-square, 147; $P < .0001$) in patients with myocardial viability demonstrated on noninvasive testing who underwent revascularization compared with medical therapy alone.⁹⁴ Furthermore, patients with viability showed a direct relationship between severity of LV dysfunction and magnitude of benefit with revascularization ($P < .001$).⁷⁹ The STICH randomized controlled trial examined 1212 patients with coronary artery disease with an LVEF of 35% or less treated with coronary artery bypass grafting (CABG) and optimal medical therapy (OMT) or OMT alone and reported no significant difference in death from any cause after 56 months of follow-up. However, CABG was superior to medical therapy for the secondary endpoints, including death from any cause or recurrent hospitalizations.⁹⁵ In contrast to prior observational studies and meta-analyses, assessment of myocardial viability in the viability substudy of the STICH trial did not identify patients with a differential survival benefit from CABG compared with OMT alone.⁹⁶ Several studies following STICH, although non-randomized, demonstrate the usefulness of viability testing before revascularization and improved survival rates in patients with viability using newer imaging modalities such as fluorodeoxyglucose positron emission tomography and cardiac magnetic resonance imaging.⁹⁷⁻⁹⁹

Most patients in the studies mentioned underwent CABG as the primary means of revascularization. Studies assessing the relative efficacy of PCI among patients with low LVEF are limited. The BARI (Bypass Angioplasty

Revascularization Investigation) study reported that the survival rate among patients with three-vessel disease and reduced LVEF (mean, $41\% \pm 6\%$) was not significantly different between CABG and percutaneous balloon angioplasty (70% vs 74%; $P = .6$). When patients with diabetes were excluded from the analysis, survival was not significantly different between CABG and percutaneous balloon angioplasty, irrespective of LVEF.¹⁰⁰ Similarly, no difference in mortality rate was noted between CABG versus PCI in 94 patients with a mean LVEF of 25% from a post hoc analysis of 454 patients in the angina with extremely serious operative mortality evaluation (AWESOME) randomized trial of CABG versus PCI who had medically refractory unstable or provokable ischemia after stabilization with medical therapy. Similar results were noted in patients with an LVEF below 35% in the nonrandomized AWESOME registry.¹⁰¹

Percutaneous coronary intervention in patients with depressed LV function is considered “high risk.” Several studies have reported increased rates of mortality, MI, stent thrombosis, and target lesion revascularization after PCI in patients with reduced LVEF.¹⁰²⁻¹⁰⁶ O’Keefe et al.¹⁰⁷ reported that among 700 patients who underwent balloon angioplasty and who were followed longitudinally, LVEF of 40% or less was a predictor of both in-hospital mortality and survival at 5-year follow-up compared with patients with preserved LV function (89% vs 81%, respectively, for survival; $P = .05$). In addition, a stepwise increase in hospital mortality rate with declining pre-PCI LVEF was noted in a retrospective study of more than 55,000 patients undergoing elective PCI. Compared with patients with preserved LVEF, odds ratios (ORs) for in-hospital mortality were .56 (95% confidence interval [CI], 1.06–2.30) for patients with an LVEF of 36% to 45%, 2.17 (95% CI, 1.42–3.31) in those with an LVEF of 26% to 35%, and 3.85 (95% CI, 2.46–6.01) for those with an LVEF of 25 or less (Figure 34.15).¹⁰⁴

Recently, the BCIS-2 trial tested whether percutaneous coronary revascularization improves event-free survival and LV function among patients with a LVEF below 35% undergoing complex PCI compared with OMT. No difference in death and heart failure hospitalizations occurred over a median of 41 months between groups (hazard ratio [HR], 0.99; 95% CI, 0.78–1.27; $P = .96$).¹⁰⁸

Careful preprocedural planning can potentially mitigate risk associated with PCI and improve both the ability to complete the procedure and clinical outcomes. Identification of high-risk patients based on patient characteristics, coronary anatomy, and clinical presentation is crucial in estimating the likelihood of technical, procedural, and clinical success of PCI. Multiple multivariable risk models have been developed and validated over the years to estimate periprocedural risk of death and MACE, all of which include reduced LVEF as a risk factor.¹⁰⁹⁻¹¹⁴ Among 5463 procedures between 1996 and 1999 in the Mayo Clinic model, five clinical and three angiographic variables predicted the occurrence of major adverse cardiac events or death, including (in decreasing predictive power) CS, left main disease, renal insufficiency, urgent or emergent procedure, NYHA functional class greater than or equal to 3, thrombus, multivessel disease, and increasing age.¹¹⁴ Similarly, the National Heart, Lung, and Blood Institute Dynamic Registry of 4448 patients revealed seven predictive variables,

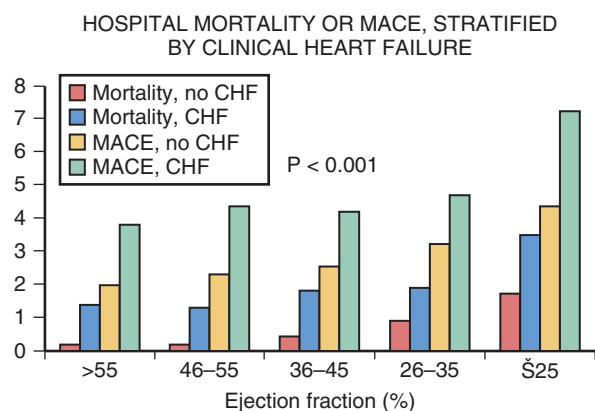


FIGURE 34.15 Hospital mortality rate or major adverse cardiac event (MACE) rate among 55,709 patients undergoing elective percutaneous coronary intervention. Reduced left ventricular ejection fraction increases the risk of hospital death or MACE. CHF, Clinical heart failure. (Reprinted with permission from Wallace TW, Berger JS, Wang A, et al. Impact of left ventricular dysfunction on hospital mortality among patients undergoing elective percutaneous coronary intervention. *Am J Cardiol.* 2009;103:355-360.)

with five of them overlapping with Mayo Clinic predictors, including (in decreasing predictive power) CS, renal insufficiency, active heart failure, attempted total coronary occlusion, urgent or emergent procedure, number of attempted lesions, and increasing age.¹¹² Other models that closely approximate the accuracy of the Mayo Clinic model include the New York state model,¹¹⁰ the Northern New England model,¹¹¹ and the Cleveland Clinic model.¹¹² A subsequent study from the Mayo Clinic that included 9035 PCIs performed on 7640 patients between 2000 and 2005 developed two risk-prediction models that successfully predicted the risk for MACE and in-hospital death. The model consisted of seven baseline clinical and noninvasive variables that included age, MI within the past 24 hours, preprocedural shock, serum creatinine, LVEF, heart failure, and peripheral artery disease.¹¹⁴

Existing risk calculators fail to capture essential components of the evaluation and management of patients with advanced heart failure referred for high-risk PCI. First, many patients with advanced heart failure have established relationships with a heart failure or transplant physician and have discussed the options of cardiac transplantation, circulatory support, or palliation. A detailed discussion with the patient and family about the risks, benefits, and alternatives to PCI, including the potential need for surgical or percutaneous circulatory support, is required. Second, any hemodynamic instability should be addressed before PCI, including management of poor systemic perfusion, pulmonary edema, hypotension, and arrhythmias. Stabilizing patients before PCI may require intravenous diuretics, inotropes, vasopressors, vasodilators, or elective endotracheal intubation. Third, most risk calculators use LVEF as a measure of heart failure severity; however, many patients with mildly depressed LVEF (40%–50%) may have severely deranged cardiac filling pressures depending on their loading conditions and therefore may be at higher risk for impaired myocardial perfusion or pulmonary congestion during high-risk PCI. Future studies examining the role of invasive hemodynamics during high-risk PCI are required. Finally, postprocedural management

of patients with advanced heart failure after PCI is equally as important as pre- and intraprocedural care. Intermittent periods of myocardial ischemia contribute to deranged hemodynamics that persist after successful coronary revascularization. For this reason, assessing the hemodynamic status after PCI should be considered. If a pMCS device is used to support PCI, weaning the device to a lower support setting and monitoring hemodynamic conditions in the catheterization laboratory may identify whether a patient is stable for decannulation of the pMCS system.

VALVULAR INTERVENTIONS IN ADVANCED HEART FAILURE

Transcatheter Aortic Valve Replacement in Advanced Heart Failure

Transcatheter aortic valve replacement (TAVR) has emerged over the past decade as an alternative to conventional surgical valve replacement in patients with severe symptomatic aortic stenosis (AS) who are deemed nonsurgical candidates because of technical considerations, and, as of 2019, is an approved therapy by the US Food and Drug Administration (FDA) across the spectrum of surgical risk.^{115,116} Indeed, by 2019, TAVR for treatment of patients with severe AS in the United States was more frequently performed than traditional surgical aortic valve replacement.¹¹⁷ Reduced LVEF is a marker of disease progression and portrays a worse outcome in patients with severe AS.¹¹⁸ Low-flow (defined as LV stroke volume index ≤ 35 mL/m²), low-gradient (transvalvular pressure gradient ≤ 40 mm Hg) severe AS occurs either in the setting of LV systolic dysfunction with reduced LVEF or because of reduced ventricular volumes and LV hypertrophy in preserved LVEF.¹¹⁹ Careful evaluation of hemodynamic changes in response to cardiac output augmentation with pharmacologic interventions using dobutamine or nitroprusside can be used to distinguish true AS from pseudostenosis. Of particular concern are patients with low flow but preserved LVEF because these patients have worse survival rates than those with normal flow (Figure 34.16).^{120,121}

Among 971 patients in the PARTNER (Placement of Aortic Transcatheter Valves) trial, low flow was observed in 55% of patients; low flow and reduced LVEF of less than 50% was observed in 23%; and low flow, low LVEF, and low gradient was observed in 15%. The 2-year mortality rate was significantly higher in patients with low flow compared with those with normal flow (47% vs 34%; HR, 1.5; 95% CI, 1.25–1.89; $P = .006$). Interestingly, low flow but not reduced LVEF or low gradient was an independent predictor of death in all patient cohorts.¹²² Similarly, low flow but not low LVEF or low gradient was noted to be an independent predictor of 30-day and 2-year death after TAVR in 334 patients with severe AS.¹²³

In the TOPAS-TAVI (Transcatheter Aortic Valve Replacement in Patients with Low-Flow, Low-Gradient Aortic Stenosis) multicenter registry, 287 patients with low-flow, low-gradient AS undergoing TAVR were included with a mean LVEF of $30.1\% \pm 9.7\%$.¹²⁴ At 1-year follow-up, LVEF had increased by 8.3% (95% CI, 6%–11%). Mortality rates in

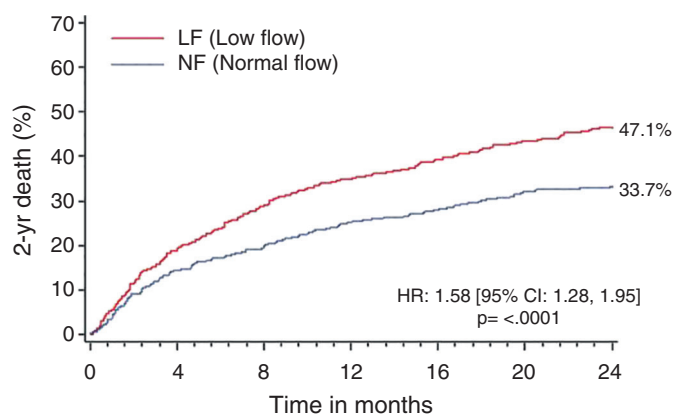


FIGURE 34.16 Kaplan-Meier all-cause mortality analysis at 2 years in patients with low flow versus normal flow. CI, Confidence interval; HR, hazard ratio. (Reused with permission from Herrmann HC, Pibarot P, Hueter I, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. *Circulation*. 2013;127:2316–2326.)

this cohort were 3.8%, 20.1%, and 32.3% at 30 days, 1 year, and 2 years, respectively (Supplemental Figure 34.1). In a multivariable analysis, chronic obstructive pulmonary disease ($P = .022$) and low hemoglobin ($P < .001$) were associated with all-cause mortality.

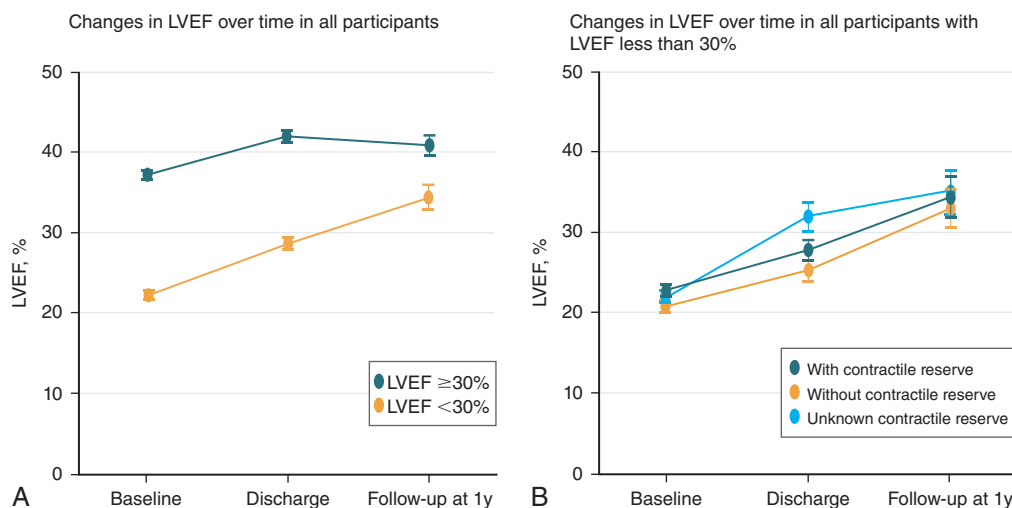
Reduced LVEF as a predictor of worse outcomes in patients with severe AS was demonstrated in some studies. In an Italian multicenter prospective study of 663 consecutive patients who underwent TAVR with the third-generation 18-Fr CoreValve device (Medtronic), the cumulative mortality rates were 5.3% at 30 days and 15% at 1 year. In addition to major access site complications, diabetes mellitus, prior stroke, and moderate to severe paravalvular leak, reduced LVEF ($<40\%$) was an independent predictor of mortality in this study, with an OR of 3.51.¹²⁵

In an analysis of the patients randomized to TAVR in the PARTNER 2 trials, 839 (28%) of the 2991-patient cohort had reduced LVEF ($<50\%$).¹²⁶ Compared with patients with

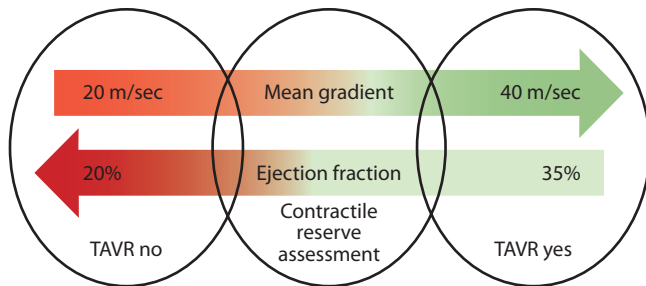
normal LVEF, those with reduced LVEF had higher rates of 2-year cardiovascular mortality (19.8% vs 12.0%; $P < .0001$) and all-cause mortality (27.4% vs 19.2%; $P < .0001$). Additionally, compared with patients with normal LVEF, patients with reduced LVEF had a higher adjusted risk of cardiovascular death (adjusted HR, 1.42; 95% CI, 1.11–1.81; $P = .005$), but not all-cause death (adjusted HR, 1.20; 95% CI, 0.99–1.47; $P = .07$) after multivariable adjustment.

Although hemodynamic optimization is critical before procedure, there is still a subset of patients who present acutely with severe AS and CS. The original randomized TAVR trials intentionally excluded patients with hemodynamic instability, defined as the use of inotropes or mechanical circulatory support.^{127,128} In an analysis of the STS/ACC TVT (Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy) registry, patients who presented between 2014 and 2017 with CS before TAVR were compared with a high-risk cohort of patients who did not present with shock. Of all-comers undergoing TAVR implantation in the United States, 4.1% presented with CS. A total of 2220 patients presented with shock (median STS, 9.8), and 12,851 patients who were deemed at high risk (median STS, 10.2) were used as the control group. Compared with the high-risk control participants, the crude 30-day all-cause mortality rate in the shock cohort was 19.1% versus 4.9%, with an adjusted HR of 3.7 (95% CI, 3.1–4.5; $P < .001$). Among those presenting with shock, the use of mechanical circulatory support, specifically cardiopulmonary bypass, was strongly associated with 30-day death.

Preprocedural planning and intraoperative considerations should be made in case hemodynamic decompensation occurs (Supplemental Figure 34.2). This includes assessment of hemodynamics with a right heart catheterization to avoid hypovolemia and to maintain adequate filling pressure, the use of inotropic support in those with reduced cardiac output or with pulmonary hypertension, and ensuring a MAP above 75 mm Hg before initiation of rapid ventricular pacing. In patients with marginal



SUPPLEMENTAL FIGURE 34-1. Outcomes from transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis in patients with reduced left ventricular ejection fraction (LVEF). **A**, Changes in LVEF over time in all participants. **B**, Changes in LVEF over time in all participants with LVEF less than 30%.



SUPPLEMENTAL FIGURE 34-2 Echocardiographic assessment of left ventricular ejection fraction, mean gradient across the aortic valve, and contractile reserve are key in predicting which patient will benefit the most from transcatheter aortic valve replacement (TAVR).

hemodynamics and reduced LVEF, consideration should be made for direct valve deployment instead of predeployment balloon valvuloplasty to avoid multiple rapid pacing runs, which can be detrimental. In addition, careful positioning of the guidewire during transapical TAVR is critical to avoid traction of the subvalvular apparatus of the mitral, leading to acute mitral regurgitation (MR). Last, a contingency plan should be in place in case of hemodynamic compromise, including percutaneous mechanical support and full cardiopulmonary bypass.

Percutaneous Approaches for Functional Mitral Regurgitation

In contrast to primary anatomic abnormalities causing regurgitation in degenerative mitral valve disease, functional mitral regurgitation (FMR) in patients with dilated cardiomyopathies results from altered LV geometry and distortion of the normal spatial relationship of the mitral valve to its subvalvular apparatus, which includes progressive mitral annular dilation, apical and lateral papillary muscle displacement, and tethering and tenting of the mitral valve leaflets.¹²⁹⁻¹³¹ Furthermore, FMR mediates further ventricular remodeling because it poses a hemodynamic load on the left ventricle, leading to progressive eccentric hypertrophy and dilation, potentially exacerbating the degree of FMR as well.^{129,132,133}

Varying degrees of FMR are virtually seen in all patients with dilated cardiomyopathy^{134,135}; however, moderate to severe FMR is seen in 17% up to 50% of patients with reduced LVEF¹³⁶⁻¹³⁸ and is considered an independent predictor of 1-year death as demonstrated in a retrospective review of more than 1200 patients with an HR of 1.85.¹²⁰ Furthermore, the presence of FMR is associated with reduced 5-year survival rate, reduced functional capacity, and increased heart failure exacerbations (Figure 34.17).^{136,139-142}

Percutaneous mitral valve repair offers an attractive alternative to surgical repair in high-risk surgical candidates. The initial large randomized, controlled trial of percutaneous MR intervention, the EVEREST II (Endovascular Valve Edge-to-Edge Repair) study, was a comparison of surgical mitral valve (MV) repair versus edge-to-edge percutaneous repair.¹⁴³ Although this trial was mainly a study of patients with primary MR, 36% of patients had a functional cause of their valvular disease. In a subgroup analysis of 65 patients with FMR, there was no difference in the

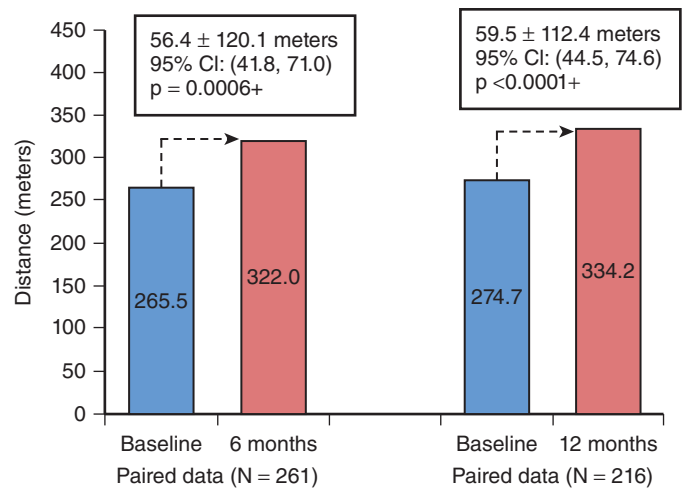


FIGURE 34.17 Changes in 6-minute walk distance from baseline to 6 and 12 months in patients with functional mitral regurgitation and degenerative mitral valve disease. (Reprinted with permission from Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol*. 2013;62(12):1052-1061, license number 3372110267854.)

primary outcome at 12 months (freedom from death, mitral valve surgery, and grade 3+ or 4+ MR) in those randomized to percutaneous versus surgical repair of the mitral valve. Despite suboptimal results compared with surgical mitral valve repair, data thus far demonstrate improved overall functional capacity and degree of residual MR with percutaneous mitral valve repair in FMR.

Based on the Alfieri technique, which creates a double mitral orifice by means of stitching the central part of the mitral valve leaflets,¹⁴⁴ percutaneous mitral valve repair using the MitraClip (Abbott Vascular) device has been available in the United States since 2013. The 4-mm-wide cobalt-chromium implant is delivered percutaneously and aligned over the origin of the regurgitant jet under fluoroscopic and transesophageal echocardiographic guidance.^{145,146} (Figure 34.18).

The largest clinical trial data comes from two randomized, controlled trials. The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial randomly assigned 614 patients with symptomatic heart failure despite maximally tolerated guideline-directed medical therapy (GDMT) and at least moderate to severe FMR to MitraClip plus OMT or to OMT alone.¹⁴⁷ The all-cause mortality rate within 2 years occurred in 29.1% of the intervention group versus 46.1% in the control group ($P < 0.001$). Additionally, the rate of heart failure hospitalizations within 2 years was 35.8% per patient-year in the intervention arm compared with 67.9% in the control arm ($P < .001$). However, results from the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) showed significantly different results. MITRA-FR randomized 304 patients with symptomatic systolic heart failure and severe FMR to MitraClip plus optimized medical therapy or to OMT alone.¹⁴⁸ The authors found there was no statistical difference between the intervention versus the control arm with regards to the mortality rate (24.3% vs 22.4%, respectively)

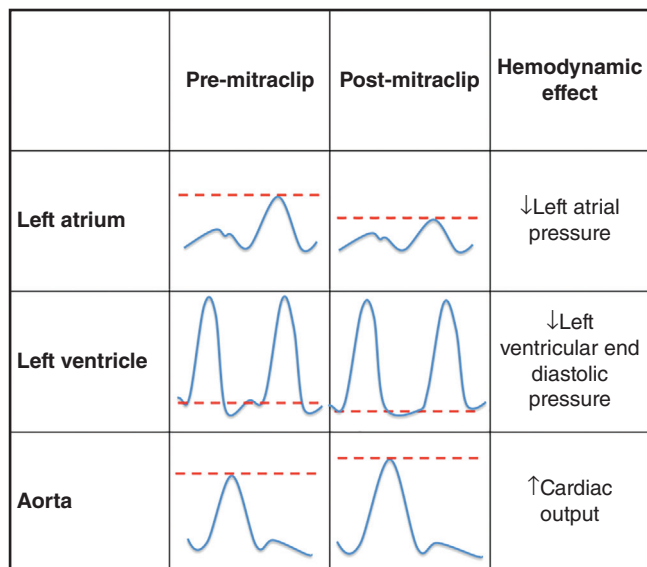


FIGURE 34.18 Optimal hemodynamic effects of MitraClip deployment. The effects include reduced left atrial (LA) pressure, reduced left ventricular end-diastolic pressure (LVEDP), and increased cardiac output.

or the rate of heart failure hospitalizations (48.7% vs 47.4%, respectively).

There were a number of differences between these two trials, which might explain the discrepancy in results. First, approximately twice as many patients were enrolled in the COAPT study than MITRA-FR. Additionally, patients enrolled in COAPT had more severe FMR and less LV dilation than those in MITRA-FR (Figure 34.19). Finally, COAPT used a central eligibility committee to adjudicate that each randomized patient was on maximally tolerated GDMT, which eliminated patients whose heart failure would improve with GDMT alone. Comparatively, in MITRA-FR, medical therapy was not optimized in all patients. This could also have been a contributor to trial outcomes. As a result of these large trial data, the

2020 ACC/AHA guidelines recommend a transcatheter edge-to-edge repair as a Class IIa recommendation in selected patients with symptomatic severe FMR and LVEF below 50% despite GDMT.¹⁴⁹ These recommendations use the COAPT trial's inclusion-exclusion criteria for optimal patient selection.

Among this cohort, some patients with severe LV dysfunction require bridging strategies while awaiting advanced therapies. An observational study published in 2020 examined the MitraBridge Registry, an international, multicenter registry of patients with at least moderate to severe FMR and advanced heart failure treated with MitraClip as a bridge.¹⁵⁰ Patients were either active on the heart transplant list or being evaluated as a bridge to decision or bridge to candidacy. Among 119 MitraClip recipients, whose mean LVEF was 26%, the 30-day survival rate was 100%. At 1-year follow-up, the rate of freedom from the composite primary endpoint (death, urgent heart transplant or LVAD, first rehospitalization for heart failure) was 64%. These data were considered encouraging for further exploration on suitable candidates for percutaneous mitral valve intervention in patients with advanced heart failure.

Other percutaneous repair or replacement devices for the treatment of patients with native mitral valve disease have yet to be approved by the FDA. Among them are numerous transcatheter replacement devices in various stages of development (Intrepid [Medtronic], Evoque [Edwards Lifesciences], Tendyne [Abbott Structural]), in addition to other edge-to-edge mitral repair systems (PASCAL [Edwards Lifesciences]).¹⁵¹⁻¹⁵⁴ Trials for these devices are currently ongoing.

Percutaneous Approaches for Tricuspid Valve Interventions

Tricuspid regurgitation can be a concurrent finding in patients with left-sided ventricular dysfunction and portends an unfavorable prognosis. Untreated, TR leads to worsening right heart failure, for which treatment options are

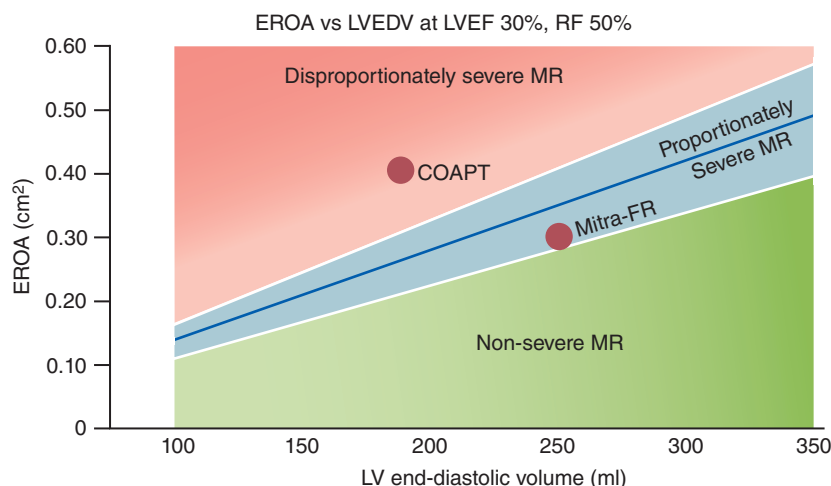


FIGURE 34.19 The relationship between effective regurgitant orifice area (EROA) and left ventricular end-diastolic volume (LVEDV), classifying functional mitral regurgitation (MR) as disproportionately severe, proportionately severe, or nonsevere. COAPT, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; LVEF, left ventricular ejection fraction; RF, regurgitant fraction.

scarce. Surgical intervention remains uncommon and is associated with the highest mortality rate among all valvular procedures, with operative mortality rates quoted between 8.8% and 9.7%.¹⁵⁵

Currently, multiple devices are being studied as percutaneous treatment options, including coaptation devices, suture or ring annuloplasty, heterotopic caval valve implants, and transcatheter tricuspid valve replacement. To date, there have been no beneficial randomized data published evaluating these tricuspid valve interventions. The TRICA-VAL (Treatment of Severe Tricuspid Regurgitation in Patients with Advanced Heart Failure with Caval Vein Implantation of the Edwards Sapien XT Valve) study, which randomized patients with severe TR and high surgical risk to either implantation with a balloon-expandable transcatheter valve into the IVC or medical therapy, was stopped early because of an unexpectedly high rate of valve dislodgements.¹⁵⁶ Based on the results of the single-arm, prospective trial to evaluate treatment with Abbott Transcatheter Clip Repair System in patients with moderate or greater tricuspid regurgitation (TRILUMINATE) study, which used the TriClip transcatheter tricuspid valve repair system (Abbott Structural), the study design for TRI-FR was recently published, in which patients with severe, symptomatic, nonsurgical, secondary TR will be randomized to either TriClip or medical therapy.^{157,158} This study is actively recruiting.

EMERGING INTERVENTIONAL APPROACHES FOR HEART FAILURE

Percutaneous Ventricular Volume Reduction

As described earlier, all existing pharmacologic and device-based therapies are designed to reduce LV “load” by optimizing LV volume and pressure. The prognostic significance of LV volume was established in the 1980s by White et al.,¹⁵⁹ who reported that a left ventricular end-systolic volume index (LVESVI) greater than 60 mL/m² is a predictor of survival after MI. A more contemporary meta-analysis showed that remodeling indices such as end-systolic volume and end-diastolic volume also predict death after therapeutic intervention for chronic systolic heart failure.¹⁶⁰ When the LVESVI exceeds 25 mL/m², OMT for heart failure offers limited benefit.¹⁶¹ Based on these observations, several studies examined the role of surgical ventricular restoration (SVR) therapy as an approach to reduce LV cavity size and improve outcomes in ischemic cardiomyopathy.¹⁶² Despite extensive registry data supporting the potential benefit of SVR, the STICH trial failed to show any benefit of CABG plus SVR over CABG alone.¹³⁷ Subsequent analysis of the STICH trial identified major limitations, including (1) enrollment of patients with relatively preserved LVEF (>35%) and no prior MI, (2) inconsistent measures of LV volumes, and (3) few patients achieving a reduction in LVESVI greater than 30% of preoperative values.¹⁶¹

The Parachute device (CardioKinetix) was a percutaneously delivered LV partitioning system composed of three main parts: a self-expanding nitinol frame, an expandable polytetrafluoroethylene (ePTFE) membrane, and an apically positioned foot. Despite initial success with clinical trials, continued development was terminated after closure of the

company. Based on the Parachute concept, the HeartTech device is now currently under clinical investigation.¹⁶² The AccuCinch (AncoraHeart) device has emerged as another novel approach to percutaneously reduce LV volume by deploying and then cinching a series of anchors below the mitral annulus via a transseptal catheter. The device is currently under clinical investigation in the clinical evaluation of the AccuCinch Ventricular Restoration System in patients who present with symptomatic heart failure with reduced ejection fraction (HFrEF) trial.

Interventions for Heart Failure with Preserved Ejection Fraction

Of the nearly 6 million individuals with heart failure in the United States, approximately half have a preserved ejection fraction above 40%. Interventions for h HFpEF are more common in older individuals (older than age 70 years); women; and patients with comorbid illnesses, which include hypertension, diabetes mellitus, coronary disease, chronic renal insufficiency, and obesity.^{7,163-165} Death caused by HFpEF approximates values associated with HFrEF; however, no therapy to specifically target HFpEF exists. The lack of treatment options is likely because the mechanisms behind HFpEF remain poorly understood. Proposed cardiac mechanisms include: ischemia, excess cardiac fibrosis, dysregulated hypertrophy, cardiomyocyte stiffness, oxidative stress, and abnormal calcium handling.^{164,165} In addition to primary cardiac causes, volume overload and vascular dysfunction contribute to HFpEF by promoting inefficient ventricular function.

Interventional approaches for HFpEF are emerging and may include the use of one-way valves positioned along the interatrial septum to offload excess volume from the left atrium by creating an interatrial shunt.¹⁶⁶ The Corvia device creates a fixed 8-mm aperture in the interatrial septum by delivered a self-expanding disk with an open barrel in the center. The reduce elevated left atrial pressure in patients with heart failure (REDUCE LAP-HF-I) trial randomized 44 patients with LVEF greater than 40% and elevated LA pressure at rest or during exercise to the Corvia device or sham procedure and reported reduced exercise-induced LA pressure elevation at 1 month of follow-up.¹⁶⁶ The REDUCE LAP-HF-II trial was a sham-controlled randomized trial design among patients with HFpEF defined by exercise hemodynamics.¹⁶⁷ Compared with sham control participants, no difference in the primary efficacy endpoint of a hierarchical composite of cardiovascular death or nonfatal ischemic stroke, total HF events, and change in health status was observed. Several additional interatrial shunt technologies are currently in development.

Novel Device-Based Approaches for Acutely Decompensated Heart Failure

More than 1 million hospitalizations are attributed to acutely decompensated heart failure (ADHF) each year in the United States alone. Current approaches for ADHF focus on intensifying diuretic therapy to achieve decongestion, which is defined by reduced total-body volume and reduced cardiac filling pressures. However, nearly 60% to 80% of patients with ADHF are discharged from the hospital with

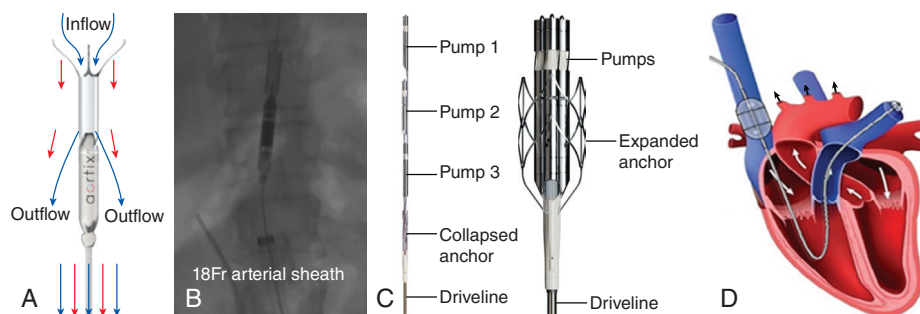


FIGURE 34.20 Emerging devices for acutely decompensated heart failure. Illustration (A) and fluoroscopic (B) images of the Aortix intraaortic rotary flow pump. C, Illustration of the ModulHeart pump system. D, Illustration of the preCARDIA device for intermittent occlusion of the superior vena cava.

persistent congestion, which is associated with increase mortality rates and risk of rehospitalization within 30 days.^{168,169} For these reasons, several technologies have emerged that are designed to enhance urine output and decongestion for patients with ADHF (Figure 34.20).¹⁷⁰ One class of technologies is impeller-based pumps placed in the descending aorta. These devices are designed to increase renal arterial pressure and urine output. The Aortix device (Procyon) is a 6.5-cm impeller pump that is 6 mm in diameter and can generate 5.0 L/min of flow. The impeller is mounted within a self-expanding nitinol strut anchoring system and is delivered transfemorally via an 18-Fr sheath. The device is connected via a 2-mm electrical lead attached to an extracorporeal motor and console.^{171,172} The SecondHeart device is a self-expanding propeller pump housed within a retractable stent that is deployed in the descending aorta and controlled via an external motor. The ModulHeart is a catheter-based pump comprised of three impellers delivered in series, then reconfigured in parallel in the descending aorta. The device is designed to provide ventricular unloading while concomitantly increasing systemic perfusion and renal perfusion. The ModulHeart recently completed first-in-human studies, which demonstrated feasibility of device delivery through a femoral approach and further showed potential to reduce cardiac filling pressures, increase cardiac output, and enhance renal perfusion.⁸⁶ All three technologies are currently under clinical investigation.

Another class of technologies improve renal perfusion and urine output by reducing central venous pressure and hence, renal vein pressure. The preCARDIA device is a balloon-mounted catheter designed to intermittently occlude the superior vena cava, thereby reducing cardiac preload and central venous pressure and increasing renal perfusion. An early feasibility and safety study demonstrated reduced bi-ventricular filling pressures and significant augmentation of urine output after 24 hours of therapy in patients with insufficient response to diuretics.¹⁷³ The Revamp device is a balloon-mounted catheter placed in the IVC that is currently under investigation. Given the increasing burden of heart failure on health care systems, novel technologies to achieve more rapid and efficient decongestion are likely to remain a primary area of development.

CONCLUSIONS

Heart failure was once considered a terminal diagnosis, and management focused on symptom management,

palliation, and the rare opportunity for cardiac transplantation. Armed with an improved understanding of the hemodynamic mechanisms governing heart failure and better invasive diagnostic and therapeutic options, the light at the end of the tunnel has become brighter for patients with advanced heart failure. The role of interventional cardiologists as integral participants of the team approach to managing patients with advanced heart failure will grow by (1) providing the ability to perform a comprehensive invasive hemodynamic and angiographic evaluation of complex pathophysiologic states, (2) understanding and communicating the clinical implications of diagnostic results, and (3) implementing advanced treatment strategies as part of a team approach for all stages and types of the heart failure spectrum. Given the growing number of patients with heart failure and increasing therapeutic options available to them, the next generation of invasive operators will be asked to think more like heart failure specialists when managing this complex patient population.

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Executive summary: heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125(1):188-197.
2. Loehr LR, Rosamond WD, Chang PP, et al. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol*. 2008;101(7):1016-1022.
3. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125(1):e2-e220.
4. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6(3):606-619.
5. INTERMACS Interagency Registry for Mechanically Assisted Circulatory Support Quarterly Statistical Report. Implant dates: June 23, 2011. Available at: <https://www.sts.org/registries/sts-national-database/intermacs-database>.
6. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2012;14(8):803-869.
7. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:e263-e421.
8. Kaye DM, Wolsk E, Nanayakkara S, et al. Comprehensive physiological modeling provides novel insights into heart failure with preserved ejection fraction physiology. *J Am Heart Assoc*. 2021;10(19):e021584.
9. Whitehead EH, Thayer KL, Sunagawa K, et al. Estimation of stressed blood volume in patients with cardiogenic shock from acute myocardial infarction and decompensated heart failure. *J Card Fail*. 2021;27(10):1141-1145.
10. Cohen M, Urban P, Christenson JT, et al. Intra-aortic balloon counterpulsation in US and non-US centres: results of the Benchmark Registry. *Eur Heart J*. 2003;24(19):1763-1770.

11. Stone GW, Ohman EM, Miller MF, et al. Contemporary utilization and outcomes of intra-aortic balloon counterpulsation in acute myocardial infarction: the benchmark registry. *J Am Coll Cardiol.* 2003;41(11):1940-1945.
12. Williams DO, Korz KS, Gewirtz H, et al. The effect of intraaortic balloon counterpulsation on regional myocardial blood flow and oxygen consumption in the presence of coronary artery stenosis in patients with unstable angina. *Circulation.* 1982;66(3):593-597.
13. Kern MJ, Aguirre F, Bach R, et al. Augmentation of coronary blood flow by intra-aortic balloon pumping in patients after coronary angioplasty. *Circulation.* 1993;87(2):500-511.
14. Kern MJ, Aguirre FV, Tatineni S, et al. Enhanced coronary blood flow velocity during intraaortic balloon counterpulsation in critically ill patients. *J Am Coll Cardiol.* 1993;21(2):359-368.
15. Braunwald E, Sarnoff SJ, Case RB, et al. Hemodynamic determinants of coronary flow: effect of changes in aortic pressure and cardiac output on the relationship between myocardial oxygen consumption and coronary flow. *Am J Physiol.* 1958;192(1):157-163.
16. Sarnoff SJ, Braunwald E, Welch GH Jr, et al. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *Am J Physiol.* 1958;192(1):148-156.
17. Sarnoff SJ, Case RB, Welch GH Jr, et al. Performance characteristics and oxygen debt in a nonfailing, metabolically supported, isolated heart preparation. *Am J Physiol.* 1958;192(1):141-147.
18. Welch GH Jr, Braunwald E, Case RB, et al. The effect of mephentermine sulfate on myocardial oxygen consumption, myocardial efficiency and peripheral vascular resistance. *Am J Med.* 1958;24(6):871-881.
19. Schreuder JJ, Castiglioni A, Donelli A, et al. Automatic intraaortic balloon pump timing using an intrabeat dirotic notch prediction algorithm. *Ann Thorac Surg.* 2005;79(3):1017-1022, discussion 1022.
20. Schreuder JJ, Maisano F, Donelli A, et al. Beat-to-beat effects of intraaortic balloon pump timing on left ventricular performance in patients with low ejection fraction. *Ann Thorac Surg.* 2005;79(3):872-880.
21. Majithia A, Jumean M, Shih H, et al. The hemodynamic effects of the MEGA intra-aortic balloon counterpulsation pump. *J Heart Lung Transplant.* 2013;32(suppl 4):S226.
22. Charitos CE, Nanas JN, Kontoyiannis DA, et al. The efficacy of the high volume counterpulsation technique at very low levels of aortic pressure. *J Cardiovasc Surg (Torino).* 1998;39(5):625-632.
23. Weber KT, Janicki JS, Walker AA. Intra-aortic balloon pumping: an analysis of several variables affecting balloon performance. *Trans Am Soc Artif Intern Organs.* 1972;18(0):486-492.
24. Papaioannou TG, Mathioulakis DS, Nanas JN, et al. Arterial compliance is a main variable determining the effectiveness of intra-aortic balloon counterpulsation: quantitative data from an in vitro study. *Med Eng Phys.* 2002;24(4):279-284.
25. Stamatiopoulos SF, Nanas JN, Saridakis NS, et al. Treating severe cardiogenic shock by large counterpulsation volumes. *Ann Thorac Surg.* 1996;62(4):1110-1117.
26. Ferguson JJ III, Cohen M, Freedman RJ Jr, et al. The current practice of intra-aortic balloon counterpulsation: results from the Benchmark Registry. *J Am Coll Cardiol.* 2001;38(5):1456-1462.
27. Eltchaninoff H, Dimas AP, Whitlow PL. Complications associated with percutaneous placement and use of intraaortic balloon counterpulsation. *Am J Cardiol.* 1993;71(4):328-332.
28. Erdogan HB, Goksedef D, Erentug V, et al. In which patients should sheathless IABP be used? An analysis of vascular complications in 1211 cases. *J Card Surg.* 2006;21(4):342-346.
29. Vallabhajosyula S, Prasad A, Bell MR, et al. Extracorporeal membrane oxygenation use in acute myocardial infarction in the United States, 2000 to 2014. *Circ Heart Fail.* 2019;12(12):e005929.
30. Becher PM, Schrage B, Sinning CR, et al. Venoarterial extracorporeal membrane oxygenation for cardiopulmonary support. *Circulation.* 2018;138(20):2298-2300.
31. Grandin EW, Nunez IJ, Willar B, et al. Mechanical left ventricular unloading in patients undergoing venoarterial extracorporeal membrane oxygenation. *J Am Coll Cardiol.* 2022;79(13):1239-1250.
32. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. *Circulation.* 2008;117(5):686-697.
33. Babaev A, Frederick PJ, Pasta DJ, et al. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA.* 2005;294(4):448-454.
34. Jeger RV, Radovanovic D, Hunziker PR, et al. Ten-year trends in the incidence and treatment of cardiogenic shock. *Ann Intern Med.* 2008;149(9):618-626.
35. Hochman JS, Buller CE, Sleeper LA, et al. Cardiogenic shock complicating acute myocardial infarction—etiologies, management and outcome: a report from the SHOCK Trial Registry. Should we emergently revascularize Occluded Coronaries for cardiogenic shock? *J Am Coll Cardiol.* 2000;36(3 suppl A):1063-1070.
36. Lindholm MG, Boesgaard S, Torp-Pedersen C, et al. Diabetes mellitus and cardiogenic shock in acute myocardial infarction. *Eur J Heart Fail.* 2005;7(5):834-839.
37. Holmes DR Jr, Berger PB, Hochman JS, et al. Cardiogenic shock in patients with acute ischemic syndromes with and without ST-segment elevation. *Circulation.* 1999;100(20):2067-2073.
38. Killip T III, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol.* 1967;20(4):457-464.
39. Forrester JS, Diamond G, Chatterjee K, et al. Medical therapy of acute myocardial infarction by application of hemodynamic subsets (second of two parts). *N Engl J Med.* 1976;295(25):1404-1413.
40. Baran DA, Grines CL, Bailey S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: this document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. *Catheter Cardiovasc Interv.* 2019;94:29-37.
41. Kapur NK, Kanwar M, Sinha SS, et al. Criteria for defining stages of cardiogenic shock severity. *J Am Coll Cardiol.* 2022;80(3):185-198.
42. Abdel-Wahab M, Saad M, Kynast J, et al. Comparison of hospital mortality with intra-aortic balloon counterpulsation insertion before versus after primary percutaneous coronary intervention for cardiogenic shock complicating acute myocardial infarction. *Am J Cardiol.* 2010;105(7):967-971.
43. Curtis JP, Rathore SS, Wang Y, et al. Use and effectiveness of intra-aortic balloon pumps among patients undergoing high risk percutaneous coronary intervention: insights from the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes.* 2012;5(1):21-30.
44. Patel MR, Smalling RW, Thiele H, et al. Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: the CRISP AMI randomized trial. *JAMA.* 2011;306(12):1329-1337.
45. Thiele H, Schuler G, Neumann FJ, et al. Intraaortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock: design and rationale of the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial. *Am Heart J.* 2012;163(6):938-945.
46. O'Neill WW, Kleiman NS, Moses J, et al. A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: the PROTECT II study. *Circulation.* 2012;126(14):1717-1727.
47. Perera D, Stables R, Clayton T, et al. Long-term mortality data from the balloon pump-assisted coronary intervention study (BCIS-1): a randomized, controlled trial of elective balloon counterpulsation during high-risk percutaneous coronary intervention. *Circulation.* 2013;127(2):207-212.
48. Perera D, Stables R, Thomas M, et al. Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. *JAMA.* 2010;304(8):867-874.
49. Cheng JM, den Uil CA, Hoeks SE, et al. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. *Eur Heart J.* 2009;30(17):2102-2108.
50. Shin TG, Choi J-H, Jo IJ, et al. Extracorporeal cardiopulmonary resuscitation in patients with in-hospital cardiac arrest: a comparison with conventional cardiopulmonary resuscitation. *Crit Care Med.* 2011;39(1):1-7.
51. Chen YS, Lin JW, Yu HY, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet.* 2008;372(9638):554-561.
52. Combes A, Leprince P, Luyt C-E, et al. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. *Crit Care Med.* 2008;36(5):1404-1411.
53. Massetti M, Tasle M, Le Page O, et al. Back from irreversibility: extracorporeal life support for prolonged cardiac arrest. *Ann Thorac Surg.* 2005;79(1):178-183, discussion 183-184.
54. Younger JG, Schreiner RJ, Swaniker F, et al. Extracorporeal resuscitation of cardiac arrest. *Acad Emerg Med.* 1999;6(7):700-707.
55. Esposito ML, Zhang Y, Qiao X, et al. Left ventricular unloading before reperfusion promotes functional recovery after acute myocardial infarction. *J Am Coll Cardiol.* 2018;72(5):501-514.
56. Kapur NK, Alkhouli MA, DeMartini TJ, et al. Unloading the left ventricle before reperfusion in patients with anterior ST-segment-elevation myocardial infarction. *Circulation.* 2019;139(3):337-346.
57. Kapur NK, Kim RJ, Moses JW, et al. Primary left ventricular unloading with delayed reperfusion in patients with anterior ST-elevation myocardial infarction: rationale and design of the STEMI-DTU randomized pivotal trial. *Am Heart J.* 2022;254:122-132.
58. Thiele H, Freund A, Gimenez MR, et al. Extracorporeal life support in patients with acute myocardial infarction complicated by cardiogenic shock—design and rationale of the ECLS-Shock trial. *Am Heart J.* 2021;234:1-11.
59. Udeson NJ, Möller JE, Lindholm MG, et al. Rationale and design of DanGer Shock: Danish-German Cardiogenic Shock trial. *Am Heart J.* 2019;214:60-68.
60. Alam M, Wardell J, Andersson E, et al. Right ventricular function in patients with first inferior myocardial infarction: assessment by tricuspid annular motion and tricuspid annular velocity. *Am Heart J.* 2000;139(4):710-715.
61. Engström AE, Vis MM, Bouma BJ, et al. Right ventricular dysfunction is an independent predictor for mortality in ST-elevation myocardial infarction patients presenting with cardiogenic shock on admission. *Eur J Heart Fail.* 2010;12(3):276-282.
62. Masci PG, Francone M, Desmet W, et al. Right ventricular ischemic injury in patients with acute ST-segment elevation myocardial infarction: characterization with cardiovascular magnetic resonance. *Circulation.* 2010;122(14):1405-1412.
63. O'Rourke RA, Dell'Italia LJ. Diagnosis and management of right ventricular myocardial infarction. *Curr Probl Cardiol.* 2004;29(1):6-47.
64. Jacobs AK, Leopold JA, Bates E, et al. Cardiogenic shock caused by right ventricular infarction: a report from the SHOCK registry. *J Am Coll Cardiol.* 2003;41(8):1273-1279.

65. Mehta SR, Eikelboom JW, Natarajan MK, et al. Impact of right ventricular involvement on mortality and morbidity in patients with inferior myocardial infarction. *J Am Coll Cardiol*. 2001;37(1):37-43.
66. Greyson CR. Pathophysiology of right ventricular failure. *Crit Care Med*. 2008;36(suppl 1):S57-S65.
67. Goldstein JA. Acute right ventricular infarction: insights for the interventional era. *Curr Probl Cardiol*. 2012;37(12):533-557.
68. John R, Lee S, Eckman P, et al. Right ventricular failure—a continuing problem in patients with left ventricular assist device support. *J Cardiovasc Transl Res*. 2010;3(6):604-611.
69. Piazza G, Goldhaber SZ. The acutely decompensated right ventricle: pathways for diagnosis and management. *Chest*. 2005;128(3):1836-1852.
70. Haddad F, Doyle R, Murphy DJ, et al. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. *Circulation*. 2008;117(13):1717-1731.
71. Patel SM, Allaire PE, Wood HG, et al. Methods of failure and reliability assessment for mechanical heart pumps. *Artif Organs*. 2005;29(1):15-25.
72. Flege JB Jr, Wright CB, Reisinger TJ. Successful balloon counterpulsation for right ventricular failure. *Ann Thorac Surg*. 1984;37(2):167-168.
73. Taylor AJ, Edwards FH, Macon MG, et al. A comparative evaluation of pulmonary artery balloon counterpulsation and a centrifugal flow pump in an experimental model of right ventricular infarction. *J Extra Corpor Technol*. 1990;22(2):85-90.
74. Nordhaug D, Steensrud T, Muller S, et al. Intraaortic balloon pumping improves hemodynamics and right ventricular efficiency in acute ischemic right ventricular failure. *Ann Thorac Surg*. 2004;78(4):1426-1432.
75. Atiemo AD, Conte JV, Heldman AW. Resuscitation and recovery from acute right ventricular failure using a percutaneous right ventricular assist device. *Catheter Cardiovasc Interv*. 2006;68(1):78-82.
76. Prutkin JM, Strote JA, Stout KK. Percutaneous right ventricular assist device as support for cardiogenic shock due to right ventricular infarction. *J Invasive Cardiol*. 2008;20(7):E215-E216.
77. Takagaki M, Wurzer C, Wade R, et al. Successful conversion of TandemHeart left ventricular assist device to right ventricular assist device after implantation of a HeartMate XVE. *Ann Thorac Surg*. 2008;86(5):1677-1679.
78. Rajdev S, Benza R, Misra V. Use of Tandem Heart as a temporary hemodynamic support option for severe pulmonary artery hypertension complicated by cardiogenic shock. *J Invasive Cardiol*. 2007;19(8):E226-E229.
79. Bajona P, Salizzoni S, Brann SH, et al. Prolonged use of right ventricular assist device for refractory graft failure following orthotopic heart transplantation. *J Thorac Cardiovasc Surg*. 2010;139(3):e53-e54.
80. Cheung A, Freed D, Hunziker P, et al. TCT-371 First clinical evaluation of a novel percutaneous right ventricular assist device: the Impella RP. *J Am Coll Cardiol*. 2012;60(17S):B106-B107.
81. Hsu PL, Parker J, Egger C, et al. Mechanical circulatory support for right heart failure: current technology and future outlook. *Artif Organs*. 2012;36(4):332-347.
82. Loor G, Khani-Hanjani A, Gonzalez-Stawinski GV. Use of RotaFlow (MAQUET) for temporary right ventricular support during implantation of HeartMate II left ventricular assist device. *ASAIO J*. 2012;58(3):275-277.
83. Kapur NK, Paruchuri V, Korabathina R, et al. Effects of a percutaneous mechanical circulatory support device for medically refractory right ventricular failure. *J Heart Lung Transplant*. 2011;30(12):1360-1367.
84. Kapur NK, Paruchuri V, Jagannathan A, et al. Mechanical circulatory support for right ventricular failure. *JACC Heart Fail*. 2013;1(2):127-134.
85. Kapur NK, Jorde UP, Sharma S, et al. Early experience with the HeartMate percutaneous heart pump from the SHIELD II trial. *ASAIO J*. 2022;68(4):492-497.
86. Vora AN, Schuyler Jones W, DeVore AD, Ebner A, Clifton W, Patel MR. First-in-human experience with Aortix intraaortic pump. *Catheter Cardiovasc Interv*. 2019;93(3):428-433.
87. Bastos MB, van Wiechen MP, Van Mieghem NM. PulseCath iVAC2L: next-generation pulsatile mechanical circulatory support. *Future Cardiol*. 2020;16(2):103-112.
88. Ragosta M, Beller GA, Watson DD, et al. Quantitative planar rest-redistribution 201Tl imaging in detection of myocardial viability and prediction of improvement in left ventricular function after coronary bypass surgery in patients with severely depressed left ventricular function. *Circulation*. 1993;87(5):1630-1641.
89. Auerbach MA, Schöder H, Hoh C, et al. Prevalence of myocardial viability as detected by positron emission tomography in patients with ischemic cardiomyopathy. *Circulation*. 1999;99(22):2921-2926.
90. Di Carli MF, Asgazzade F, Schelbert HR, et al. Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy. *Circulation*. 1995;92(12):3436-3444.
91. Marwick TH, Zuchowski C, Lauer MS, et al. Functional status and quality of life in patients with heart failure undergoing coronary bypass surgery after assessment of myocardial viability. *J Am Coll Cardiol*. 1999;33(3):750-758.
92. Pagley PR, Beller GA, Watson DD, et al. Improved outcome after coronary bypass surgery in patients with ischemic cardiomyopathy and residual myocardial viability. *Circulation*. 1997;96(3):793-800.
93. Meluzin J, Cerny J, Frélich M, et al. Prognostic value of the amount of dysfunctional but viable myocardium in revascularized patients with coronary artery disease and left ventricular dysfunction. Investigators of this Multi-center Study. *J Am Coll Cardiol*. 1998;32(4):912-920.
94. Allman KC, Shaw LJ, Hachamovitch R, et al. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol*. 2002;39(7):1151-1158.
95. Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med*. 2011;364(17):1607-1616.
96. Bonow RO, Maurer G, Lee KL, et al. Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med*. 2011;364(17):1617-1625.
97. Kwon DH, Hachamovitch R, Popovic ZB, et al. Survival in patients with severe ischemic cardiomyopathy undergoing revascularization versus medical therapy: association with end-systolic volume and viability. *Circulation*. 2012;126(11 suppl 1):S3-S8.
98. Gerber BL, Rousseau MF, Ahn SA, et al. Prognostic value of myocardial viability by delayed-enhanced magnetic resonance in patients with coronary artery disease and low ejection fraction: impact of revascularization therapy. *J Am Coll Cardiol*. 2012;59(9):825-835.
99. Ling LF, Marwick TH, Flores DR, et al. Identification of therapeutic benefit from revascularization in patients with left ventricular systolic dysfunction: inducible ischemia versus hibernating myocardium. *Circ Cardiovasc Imaging*. 2013;6(3):363-372.
100. Chaitman BR, Rosen AD, Williams DO, et al. Myocardial infarction and cardiac mortality in the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial. *Circulation*. 1997;96(7):2162-2170.
101. Sedlis SP, Ramanathan KB, Morrison DA, et al. Outcome of percutaneous coronary intervention versus coronary bypass grafting for patients with low left ventricular ejection fractions, unstable angina pectoris, and risk factors for adverse outcomes with bypass (the AWESOME Randomized Trial and Registry). *Am J Cardiol*. 2004;94(1):118-120.
102. Sardi GL, Gaglia MA Jr, Maluenda G, et al. Outcome of percutaneous coronary intervention utilizing drug-eluting stents in patients with reduced left ventricular ejection fraction. *Am J Cardiol*. 2012;109(3):344-351.
103. Goto M, Kohsaka S, Aoki N, et al. Risk stratification after successful coronary revascularization. *Cardiovasc Revasc Med*. 2008;9(3):132-139.
104. Wallace TW, Berger JS, Wang A, et al. Impact of left ventricular dysfunction on hospital mortality among patients undergoing elective percutaneous coronary intervention. *Am J Cardiol*. 2009;103(3):355-360.
105. Keelan PC, Johnston JM, Koru-Sengul T, et al. Comparison of in-hospital and one-year outcomes in patients with left ventricular ejection fractions $\leq 40\%$, 41% to 49% , and $\geq 50\%$ having percutaneous coronary revascularization. *Am J Cardiol*. 2003;91(10):1168-1172.
106. Lindsay J Jr, Grasa G, Pinnow EE, et al. Procedural results of coronary angioplasty but not late mortality have improved in patients with depressed left ventricular function. *Clin Cardiol*. 1999;22(8):533-536.
107. O'Keefe JH Jr, Rutherford BD, McConahay DR, et al. Multivessel coronary angioplasty from 1980 to 1989: procedural results and long-term outcome. *J Am Coll Cardiol*. 1990;16(5):1097-1102.
108. Perera D, Clayton T, O'Kane PD, et al. Percutaneous revascularization for ischemic left ventricular dysfunction. *N Engl J Med*. 2022;387(15):1351-1360.
109. Ellis SG, Weintraub W, Holmes D, et al. Relation of operator volume and experience to procedural outcome of percutaneous coronary revascularization at hospitals with high interventional volumes. *Circulation*. 1997;95(11):2479-2484.
110. Hannan EL, Racz M, Ryan TJ, et al. Coronary angioplasty volume-outcome relationships for hospitals and cardiologists. *JAMA*. 1997;277(11):892-898.
111. O'Connor GT, Malenka DJ, Quinton H, et al. Multivariate prediction of in-hospital mortality after percutaneous coronary interventions in 1994-1996. Northern New England Cardiovascular Disease Study Group. *J Am Coll Cardiol*. 1999;34(3):681-691.
112. Holmes DR, Selzer F, Johnston JM, et al. Modeling and risk prediction in the current era of interventional cardiology: a report from the National Heart, Lung, and Blood Institute Dynamic Registry. *Circulation*. 2003;107(14):1871-1876.
113. Singh M, Rihal CS, Lennon RJ, et al. Bedside estimation of risk from percutaneous coronary intervention: the new Mayo Clinic risk scores. *Mayo Clin Proc*. 2007;82(6):701-708.
114. Singh M, Lennon RJ, Holmes DR Jr, et al. Correlates of procedural complications and a simple integer risk score for percutaneous coronary intervention. *J Am Coll Cardiol*. 2002;40(3):387-393.
115. Zajarias A, Cribier AG. Outcomes and safety of percutaneous aortic valve replacement. *J Am Coll Cardiol*. 2009;53(20):1829-1836.
116. Coylewright M, Forrest J, McCabe J, et al. TAVR in low-risk patients. *J Am Coll Cardiol*. 2020;75(10):1208-1211.
117. Carroll JD, Mack MJ, Vemulapalli S, et al. STS-ACC TVT registry of transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2020;76:2492-2516.
118. Lund O, Fløe C, Jensen FT, et al. Left ventricular systolic and diastolic function in aortic stenosis. Prognostic value after valve replacement and underlying mechanisms. *Eur Heart J*. 1997;18(12):1977-1987.
119. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2008;118(15):e523-e661.
120. Clavel M-A, Dumesnil JG, Capoulade R, et al. Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2012;60(14):1259-1267.
121. Hachicha Z, Dumesnil JG, Bogaty P, et al. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated

- with higher afterload and reduced survival. *Circulation*. 2007;115(22):2856-2864.
122. Herrmann HC, Pibarot P, Hueter I, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. *Circulation*. 2013;127(23):2316-2326.
 123. Le Ven F, Freeman M, Webb J, et al. Impact of low flow on the outcome of high-risk patients undergoing transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2013;62(9):782-788.
 124. Ribeiro HB, Lerakis S, Gilard M, et al. Transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis: the TOPAS-TAVI Registry. *J Am Coll Cardiol*. 2018;71(12):1297-1308.
 125. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation*. 2011;123(3):299-308.
 126. Furer A, Chen S, Redfors B, et al. Effect of baseline left ventricular ejection fraction on 2-year outcomes after transcatheter aortic valve replacement: analysis of the PARTNER 2 trials. *Circ Heart Fail*. 2019;12(8):e005809.
 127. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597-1607.
 128. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol*. 2014;63:1972-1981.
 129. Lancellotti P, Marwick T, Pierard LA. How to manage ischaemic mitral regurgitation. *Heart*. 2008;94(11):1497-1502.
 130. Trichon BH, O'Connor CM. Secondary mitral and tricuspid regurgitation accompanying left ventricular systolic dysfunction: is it important, and how is it treated? *Am Heart J*. 2002;144(3):373-376.
 131. Yiu SF, Enriquez-Sarano M, Tribouilloy C, et al. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. *Circulation*. 2000;102(12):1400-1406.
 132. Spoor MT, Geltz A, Bolling SF. Flexible versus nonflexible mitral valve rings for congestive heart failure: differential durability of repair. *Circulation*. 2006;114(suppl 1):167-171.
 133. Romano MA, Bolling SF. Update on mitral repair in dilated cardiomyopathy. *J Card Surg*. 2004;19(5):396-400.
 134. Koelling TM, Aaronson KD, Cody RJ, et al. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. *Am Heart J*. 2002;144(3):524-529.
 135. Strauss RH, Stevenson LW, Dadourian BA, et al. Predictability of mitral regurgitation detected by Doppler echocardiography in patients referred for cardiac transplantation. *Am J Cardiol*. 1987;59(8):892-894.
 136. Agricola E, Stella S, Figini F, et al. Non-ischemic dilated cardiomyopathy: prognostic value of functional mitral regurgitation. *Int J Cardiol*. 2011;146(3):426-428.
 137. Jones RH, Velazquez EJ, Michler RE, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med*. 2009;360(17):1705-1717.
 138. Bouma W, van der Horst IC, Wijdh-den Hamer IJ, et al. Chronic ischaemic mitral regurgitation. Current treatment results and new mechanism-based surgical approaches. *Eur J Cardiothorac Surg*. 2010;37(1):170-185.
 139. Lamas GA, Mitchell GF, Flaker GC, et al. Clinical significance of mitral regurgitation after acute myocardial infarction. Survival and Ventricular Enlargement Investigators. *Circulation*. 1997;96(3):827-833.
 140. Bursi F, Enriquez-Sarano M, Nkomo VT, et al. Heart failure and death after myocardial infarction in the community: the emerging role of mitral regurgitation. *Circulation*. 2005;111(3):295-301.
 141. Grigioni F, Detaint D, Avierinos J-F, et al. Contribution of ischemic mitral regurgitation to congestive heart failure after myocardial infarction. *J Am Coll Cardiol*. 2005;45(2):260-267.
 142. Grigioni F, Enriquez-Sarano M, Zehr KJ, et al. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation*. 2001;103(13):1759-1764.
 143. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364(15):1395-1406.
 144. Alfieri O, Maisano F, De Bonis M, et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg*. 2001;122(4):674-681.
 145. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. *J Am Coll Cardiol*. 2009;54(8):686-694.
 146. Silvestry FE, Rodriguez LL, Herrmann HC, et al. Echocardiographic guidance and assessment of percutaneous repair for mitral regurgitation with the Evalve MitraClip: lessons learned from EVEREST I. *J Am Soc Echocardiogr*. 2007;20(10):1131-1140.
 147. Stone GW, Lindenfeld J, Abraham T, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307-2318.
 148. Obadia J-F, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medial treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379:2297-2306.
 149. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143(5):e35-e71.
 150. Godino C, Munafò A, Scotti A, et al. MitraClip in secondary mitral regurgitation as a bridge to heart transplantation: 1-year outcomes from the International MitraBridge Registry. *J Heart Lung Transplant*. 2020;39(12):1353-1362.
 151. Bapat V, Rajagopal V, Meduri C, et al. Early experience with new transcatheter mitral valve replacement. *J Am Coll Cardiol*. 2018;71:12-21.
 152. Beller JP, Rogers JH, Thourani VH, Ailawadi G. Early clinical results with the Tendyne transcatheter mitral valve replacement system. *Ann Cardiothorac Surg*. 2018;7:776-779.
 153. Webb J, Hensey M, Fam N, et al. Transcatheter mitral valve replacement with the transseptal EVOQUE system. *JACC Cardiovasc Interv*. 2020;13:2418-2426.
 154. Webb JG, Hensey M, Szerlip M, et al. One-year outcomes for transcatheter repair in patients with mitral regurgitation from the CLASP Study. *JACC Cardiovasc Interv*. 2020;13(20):2344-2357.
 155. Asmarats L, Puri R, Latib A, et al. Transcatheter TRicuspid valve interventions: landscape, challenges, and future directions. *J Am Coll Cardiol*. 2018;71(25):2935-2956.
 156. Dreger H, Mattig I, Hewing B, et al. Treatment of severe TRicuspid regurgitation in patients with advanced heart failure with CAval vein implantation of the Edwards Sapien XT VALVE (TRICAVAL): a randomised controlled trial. *EuroIntervention*. 2020;15(17):1506-1513.
 157. Lurz P, Stephan von Bardeleben R, Weber M, et al. Transcatheter edge-to-edge repair for treatment of tricuspid regurgitation. *J Am Coll Cardiol*. 2021;77(3):229-239.
 158. Donal E, Leurent G, Ganivet A, et al. Multicentric randomized evaluation of a tricuspid valve percutaneous repair system (clip for the tricuspid valve) in the treatment of severe secondary tricuspid regurgitation Tri.Fr Design paper. *Eur Heart J Cardiovasc Imaging*. 2022;23(12):1617-1627.
 159. White HD, Norris RM, Brown MA, et al. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation*. 1987;76(1):44-51.
 160. Kramer DG, Trikalinos TA, Kent DM, et al. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. *J Am Coll Cardiol*. 2010;56(5):392-406.
 161. Buckberg G, Athanasuleas C, Conte J. Surgical ventricular restoration for the treatment of heart failure. *Nat Rev Cardiol*. 2012;9(12):703-716.
 162. Zhu Z, Yu J, Xu K, et al. First-in-man study of Heartech® percutaneous left ventricular partitioning device for treatment of heart failure postmyocardial infarction. *Catheter Cardiovasc Interv*. 2019;94:845-853.
 163. Bench T, Burkhoff D, O'Connell JB, et al. Heart failure with normal ejection fraction: consideration of mechanisms other than diastolic dysfunction. *Curr Heart Fail Rep*. 2009;6(1):57-64.
 164. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011;32(6):670-679.
 165. Grossman W, Paulus WJ. Myocardial stress and hypertrophy: a complex interface between biophysics and cardiac remodeling. *J Clin Invest*. 2013;123(9):3701-3703.
 166. Feldman T, Mauri L, Kahwash R, et al. Transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients With Heart Failure]): a phase 2, randomized, sham-controlled trial. *Circulation*. 2018;137:364-375.
 167. Shah SJ, Borlaug BA, Chung ES, et al. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. *Lancet*. 2022;399(10330):1130-1140.
 168. Arrigo M, Jessup M, Mullens W, et al. Acute heart failure. *Nat Rev Dis Primers*. 2020;6:16.
 169. Cooper LB, Mentz RJ, Stevens SR, et al. Hemodynamic predictors of heart failure morbidity and mortality: fluid or flow? *J Card Fail*. 2016;22:182-189.
 170. Rosenblum H, Kapur NK, Abraham WT, et al. Conceptual considerations for device-based therapy in acute decompensated heart failure: DRI₂P₂S. *Circ Heart Fail*. 2020;13:e006731.
 171. Annamalai SK, Esposito ML, Reyelt LA, et al. Abdominal positioning of the next-generation intra-aortic fluid entrainment pump (Aortix) improves cardiac output in a Swine Model of heart failure. *Circ Heart Fail*. 2018;11(8):e005115.
 172. Vora AN, Jones WS, DeVore AD, Ebner A, Clifton W, Patel MR. First-in-human experience with Aortix intraaortic pump. *Catheter Cardiovasc Interv*. 2019;93(3):428-433.
 173. Kapur NK, Kiernan MS, Gorgoshvili I, et al. Intermittent occlusion of the superior vena cava to improve hemodynamics in patients with acutely decompensated heart failure: the VENUS-HF Early Feasibility Study. *Circ Heart Fail*. 2022;15(2):e008934.

**INTRODUCTION, 650**DEVELOPMENT OF THE PROCEDURE:
HISTORICAL PERSPECTIVE, 651

TECHNIQUE OF THE PROCEDURE, 652

SAFETY OF ENDOMYOCARDIAL
BIOPSY, 653PROCESSING ENDOMYOCARDIAL TISSUE
SPECIMENS, 655INDICATIONS FOR ENDOMYOCARDIAL
BIOPSY, 656ENDOMYOCARDIAL BIOPSY IN CARDIAC
TRANSPLANT ALLOGRAFTS, 659

EXPERT PRACTICE SUMMARY, 660

CONCLUSIONS, 660

Dr. Deepak L. Bhatt discloses the following relationships: Advisory Board: Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, Stasys; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Novartis, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair),

VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, 89Bio; Royalties: Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Philips, Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Takeda.

INTRODUCTION

Endomyocardial biopsy (EMB) has long been used in patients with cardiovascular conditions to diagnose disease, guide treatments, and assist with prognostication. To better understand the role of this invasive diagnostic procedure, it is important to review its history, approach to patients, safety, and utility. Assessment of the risk-to-benefit ratio of the procedure depends on understanding the procedure's nuances, particularly what the diagnostic capabilities are and risks. Clinicians, investigators, and professional societies have all addressed this issue, and guideline recommendations to help with expert clinical practice have been published. In particular, a scientific statement from the American Heart Association (AHA) and the European Society of Cardiology (ESC; endorsed by the Heart Failure Society of America and the Heart Failure Association of the ESC) was published in 2007.¹ Although now slightly dated, it remains an outstanding overview of the procedure but with limited coverage of newer noninvasive techniques for myocardial pathologic diagnoses. A more recent overview of the subject came out more than a decade ago in 2012 with a particular focus on the role of pathologists and pathologic specimens in certain clinical

situations.² This reference contains numerous figures with colorful examples of myocardial pathology and notes in the conclusion the procedure is the “gold standard” for the diagnosis of cardiac allograft rejection, myocarditis, and infiltrative and storage diseases and can be helpful in unexplained pathological conditions. The most recent consensus document published in 2021 was from the Heart Failure Association, Heart Failure Society of America, and the Japanese Heart Failure Society.³ This statement commented in more detail on the role of a variety of noninvasive cardiac imaging and other techniques that might take the place of endomyocardial biopsy or augment diagnostic insight when attempting to diagnose, for example, amyloidosis, myocarditis, and sarcoidosis. Understanding these issues when planning a patient’s evaluation is critical. Clearly, endomyocardial biopsy remains an important diagnostic tool in cardiologists’ armamentarium, but it is important to know when to choose this approach.

DEVELOPMENT OF THE PROCEDURE: HISTORICAL PERSPECTIVE

Linking pathologic information obtained during postmortem examination of the heart or tissue specimens removed at the time of cardiac surgery has given insight into myocardial pathology.² Relating these findings to clinical scenarios is a foundation of medical practice. Histologic, histobiochemical, immune histochemical, and nuclear protein analysis of cardiac tissue can more precisely characterize disease in many patients premortem, particularly when a clinical diagnosis is challenging to make. However, examination of biopsy specimens could only be performed after cardiac tissue was obtained at the time of thoracic or beating heart surgery. In the 1950s, a limited thoracotomy approach was sometimes used to obtain samples of myocardium. The first percutaneous, nonsurgical, transthoracic, needle biopsy approaches to heart biopsy were reported in the late 1950s and 1960s.⁴⁻⁸ These adventures were associated with an incidence of major complications, including cardiac tamponade, coronary artery laceration, and pneumothorax, in almost 10% of procedures, much more common than noted in contemporary studies. Direct percutaneous needle biopsy of the heart was limited by fear of these complications as well as the difficulty of obtaining an adequate amount of tissue when using relatively small needle puncturing and cutting devices developed more for liver and kidney biopsy. Also, the beating heart with a high pressure blood-filled system proved a difficult target. Multiple passes into the myocardium to obtain adequate tissue increased risk. Suttone et al.’s⁸ report of a percutaneous transthoracic biopsy approach noted that insufficient tissue for examination was the outcome in almost one-quarter of the patients. Often, no endomyocardial tissue could be obtained during these procedures. It was the development of a biptome that could be used with a transvenous or transarterial approach to the right or left ventricle via the left basilica and either femoral vein or from the left axillary or either femoral artery and then into the heart that first allowed more reliable examination of adequate endomyocardial tissue. More recently, left

ventricular (LV) endomyocardial biopsy has been safely performed via radial artery access. This approach was thought preferable because an LV endomyocardial biopsy was believed safer without the potential for tricuspid valve damage with per-venous right atrial or right ventricular approaches and more likely to deliver adequate tissue, allowing for a higher diagnostic yield. Another contemporary approach with limited evaluation but interesting possibilities include a coronary sinus catheter sheath placed via a subclavian vein and passed across the tricuspid valve only once. The biptome can then be repeatedly passed through the sheath and across the tricuspid valve with, perhaps, less risk of valve damage.⁹ Progress continues, but until reliable and adequate endomyocardial tissue could be obtained, diagnoses could only be made after autopsy or direct surgical recovery of specimens.

Setting the stage for today’s more recent advances, Sakakibara and Konno¹⁰ used a flexible biptome with retractable and then grasping terminus cutting cusps to pinch off pieces of myocardium during an endovascular approach to the left ventricle. Subsequently, Caves et al., using a modified Konno biopsy forceps (subsequently coming to be known as the Stanford Caves-Shulz biptome, which evolved to the Scholten apparatus), to obtain tissue after passing the instrument through the right internal jugular vein with only local anesthesia used, and rapid tissue retrieval. Improved devices promoted procedure safety and success.⁷⁻¹² The motivation for development of the Stanford Caves-Shulz biptome was diagnosing cardiac transplant allograft rejection so that immunosuppression could be modified to optimize transplant heart function and prevent or treat potentially catastrophic rejection. This tool was reusable and underwent subsequent modification that improved tissue biopsy while becoming the standard management system for heart transplant patients that subsequently morphed into multiple disposable and reusable instruments used today.¹¹ The Stanford Caves-Shulz system had an advantage over the Konno biptome in that it did not require a cutdown to facilitate entry into the saphenous or basilic vein (or the femoral or brachial artery if LV tissue was the target).¹² With fluoroscopic or echocardiographic imaging, the biptome could be safely advanced to the endocardial surface with the jaws closed, the catheter slightly withdrawn, and the jaws opened followed by the catheter’s being readvanced onto the endocardial surface (usually signaled by premature ventricular contractions, ectopy couplets, or short runs of nonsustained ventricular tachycardia). After closure of the clasps and then gentle tugging back the closed-jaw biptome, withdrawal of tissue was usually successful and a few cubic millimeters in size. Crush artifact was not often a problem, and unless significant fibrotic endocardium was at the biopsy site, adequate samples of heart tissue were obtained. The Stanford Caves-Shulz biptome could be used for many procedures (often >50) without reconstructive maintenance or sharpening. Subsequently, the King biptome became used as well and was a modification of biopsy forceps used for transbronchial biopsy.¹²⁻¹⁵ This flexible shaft biptome could be introduced through a catheter into the right or left ventricle, and using the same technique with the jaw-opening mechanism, allowed

retrieval of several samples from slightly varying locations in the ventricle during several reinsertions and passes at the myocardium. Subsequent modification of biopsy catheters allowed disposal of single-use biotomes and improved flexibility, which allowed greater percutaneous positioning and mobility of the catheter.

TECHNIQUE OF THE PROCEDURE

The right internal jugular vein is most commonly accessed with a puncture and sheath-based catheter system for right ventricular (RV) endomyocardial biopsy (see earlier commentary about additional approaches).¹³⁻¹⁷ Some experts routinely approach the patient by accessing the femoral vein using longer biotomes and sheath systems. This approach has the disadvantage of requiring the patient to remain supine for some time after the procedure to ensure that the puncture site does not bleed. Usually when doing the procedure from the neck or subclavian site, the patient can sit up and walk immediately after biopsy. Also, this approach, because the catheter system is quite long, makes manipulation and proper placement of the biotome in the ventricle more challenging. Using sonographic imaging of the internal jugular vein has remarkably decreased the challenges of doing endomyocardial biopsy. The number of attempts required for successful venipuncture, complications, and duration of the procedure have been improved with the ability to image the great veins of the neck and mediastinum by facilitating determination of vessel size, patency, and phasic respiratory variation of the target and location.¹⁷⁻²³ Of course, ultrasound guidance for femoral vein puncture can also be used and might be particularly helpful in patients who have unusual femoral triangle anatomy or scarring in this region from prior catheterization procedures. For central venous puncture, some operators place the patient in a reverse Trendelenburg position during the internal jugular vein approach to facilitate venous engorgement or simply place a wedging device under the patient's legs. This should be removed after successful venous access has been achieved, particularly if right heart hemodynamic measurements are to be assessed. Having the patient do a Valsalva maneuver during the puncture to engorge and expand the internal jugular vein to a more sizeable dimension may facilitate safe and successful vascular access. During the procedure, the patient is monitored from electrocardiographic, systemic blood pressure, and pulse oximetric perspectives. If the internal jugular venous system is atretic or occluded for one reason or another, the subclavian vein is an option (see earlier commentary). With a natural "C" curvature formed with the biotome, use of the left subclavian vein seems preferable to the right, although both approaches are relatively straightforward and feasible. If LV tissue, for one reason or another, is desirable, the approach usually uses a sheath placed into a femoral artery; however, as noted earlier, the radial artery approach is also an option. Constant positive pressure is maintained during this approach to avoid blood stasis and clot formation within the sheath with its risk of subsequent embolization, particularly when the system end hole is in the left ventricle or

aortic arch. The sheath system can be pushed across the aortic valve and positioned near the endocardium with the biotome and then passed repeatedly through it to obtain samples, again with care taken to avoid air or thrombus embolization.

Guidance of the biopsy catheter into the heart is generally done under fluoroscopic surveillance in a cardiac catheterization laboratory or radiologic procedure room, but two-dimensional echocardiography has also been used.²⁰⁻²² Portable echocardiographic and fluoroscopic units can facilitate biopsy procedures being done at the bedside, usually in an intensive care unit for critically ill, hospitalized patients. Arguably, fluoroscopy generally provides more information than echocardiography (some biotomes commercially available are not very echogenic). With the patient in the posteroanterior fluoroscopic view, the course of the biotome through the great thoracic vessels as it crosses the tricuspid or aortic valve and then enters the right or LV cavity can be monitored ([Figure 35.1](#) and [Video 35.1A](#)). During fluoroscopy, the image can be rotated into the left anterior oblique position to assist with confirmation that biotome jaws are facing the interventricular septum rather than the free LV wall ([Figure 35.2](#) and [Video 35.1B](#)). The main challenge of echocardiographic-guided endomyocardial biopsy is imaging the biotome, particularly the jaws of the device. This can be a function of the device echogenicity and the ease of obtaining echocardiographic images in any particular patient. When successful images are obtained, endomyocardial biopsy can be made safer and provide better target images. An apical four chamber-transthoracic echocardiographic view can allow a panoramic image of the right ventricle and help with target identification for the biotome jaws. It is important to avoid the free RV wall, if at all possible, to decrease the likelihood of ventricular perforation. This is particularly important in nonheart transplant patients ([Video 35.1C](#)). Also helpful is the fact that echocardiographic images can identify the papillary muscles and give

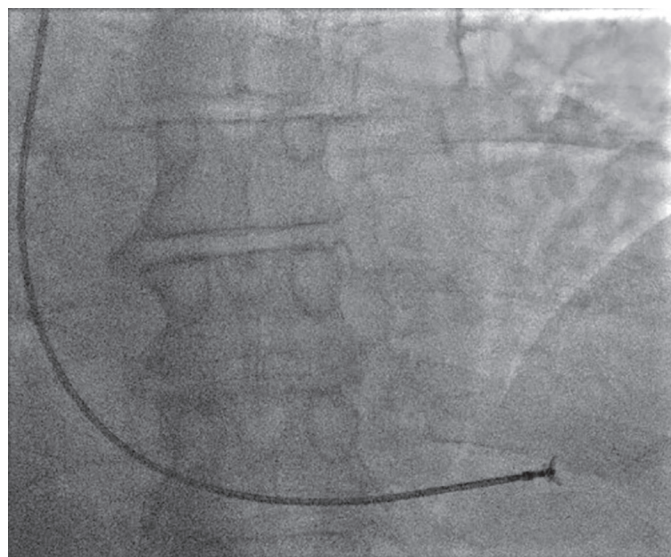


FIGURE 35.1 The posteroanterior projection used to position the biotome in the right ventricle.

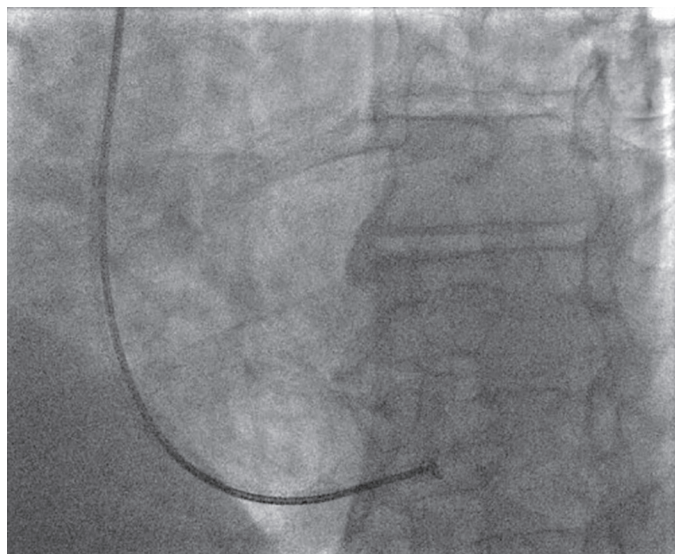


FIGURE 35.2 The left anterior oblique projection used to confirm the bioprobe is facing the right ventricular septum.

insight into where chordae tendineae might lie such that biopsy of these structures (particularly the tip of the papillary muscle) is avoided, specifically in the cardiac allograft, where multiple biopsies over time are required. Another approach to lessening the risk of biopsy-induced tricuspid insufficiency is to use a longer sheath system, one which can be placed as a guiding sheath across the tricuspid valve. This would likely prevent damage to the valve itself from the rigid and relatively unforgiving bioprobe as it is pushed through the tricuspid valve. Perhaps this is more important when repeated biopsies are done on a cardiac allograft, but some would argue that it is more important when doing a biopsy in a native heart. Unfortunately, sometimes when the sheath is left across the tricuspid valve during the biopsy procedure it limits mobility of the bioprobe when it is trying to be placed against the RV target. With either fluoroscopic or echocardiographic guidance, after confirmation that the bioprobe jaws are opposing the interventricular septum, the device is advanced into the septum, premature ventricular contractions are induced (usually) with the jaws then quickly and firmly closed, and the specimen is removed with a gentle tug ([Video 35.1D](#)).

Using both fluoroscopic and echocardiographic monitoring when a specific location in the ventricle is the target can be helpful ([Figure 35.3](#) and [Video 35.2](#)). Before the biopsy procedure, computed tomography or cardiac magnetic resonance (CMR) imaging of the heart might be helpful with making a pathologic diagnosis and give the operator insight into precise cardiac anatomy, particularly the angle of the intraventricular septum in relationship to the superior or inferior vena cava, and specific location of target areas for biopsy.²⁰⁻²³ Knowledge of anatomic relationships characterized by multimodal imaging may lessen the risk of inadvertent free RV wall biopsy during a fluoroscopic-directed procedure, which could decrease the likelihood of RV perforation and subsequent problematic pericardial effusion and cardiac tamponade. It should

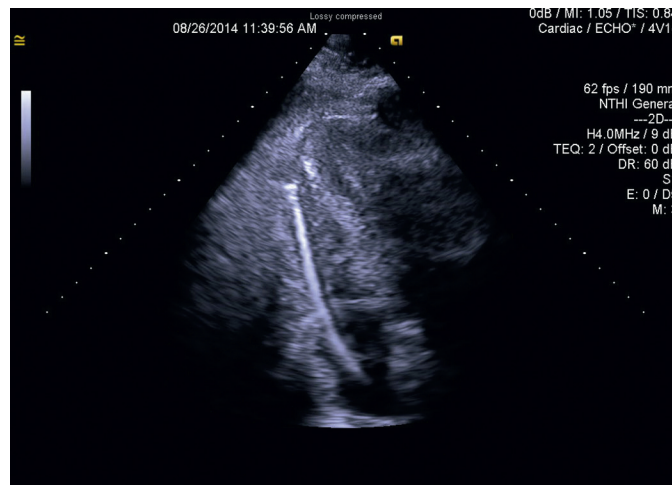


FIGURE 35.3 Echocardiography shows that the bioprobe is pointing toward the right ventricular (RV) free wall and needs to be repositioned toward the RV septum.

be noted that using CMR to help target focal disease location that might allow bioprobe navigation into areas of interest is challenging. Three-dimensional echocardiography has also been used to assist with the procedure and obviate the need for fluoroscopy, but limited data are available comparing this approach with the others.

SAFETY OF ENDOMYOCARDIAL BIOPSY

Today the majority of endomyocardial biopsies are done to monitor cardiac allograft rejection after heart transplant.²³⁻²⁹ This relates to the importance of knowing allograft rejection status, relative safety of the procedure, and reasonable diagnostic accuracy. As with any invasive technique, the likelihood of an adverse event seems to depend on the experience of the operator and team doing the procedure.²³⁻²⁵ This is further influenced by the clinical status or stability of the patient, bioprobe used, vascular access approach chosen, presence or absence of left bundle branch block, location in the ventricle biopsied, and underlying disease. [Table 35.1](#) summarizes potential difficulties occurring during endomyocardial biopsy. Risks that develop acutely include problems associated with vascular access such as inadvertent puncture of central or peripheral arteries, biopsy site hematoma formation, creation of peripheral arteriovenous fistula, or arteriovenous fistulae within the heart itself related to coronary artery injury.^{3,25} One usually transient and generally minor difficulty is nerve paralysis related to anesthesia infiltration of tissue overlying the vascular access site with dissection down the arteriovenous tissue sheath running into the mediastinum, where recurrent laryngeal nerve paralysis can develop. Ventricular or supraventricular arrhythmias can be seen, including paroxysmal supraventricular tachycardia and atrial fibrillation (usually transient) as well as isolated ventricular arrhythmias, sustained ventricular tachycardia, and ventricular fibrillation with frank cardiac

TABLE 35.1 Risks of Endomyocardial Biopsy: Potential Difficulties

- Vascular access
 - Inadvertent arterial puncture while obtaining venous access
 - Horner's syndrome (hoarseness with unilateral ptosis, injected conjunctiva, anisocoria, and anhidrosis of the face) caused by caudal migration of local anesthetic when inadvertently injected into the carotid; the internal jugular vascular sheath with sympathetic and parasympathetic nerve action is disrupted
 - Vasovagal reaction
 - Air embolism during internal jugular approach
 - Puncture site bleeding and neck hematoma
 - Pneumothorax
- Biopsy procedure
 - Innominate vein perforation
 - Tricuspid valve injury
 - Tricuspid valve leaflet injury/perforation
 - Severing tricuspid valve chordae tendineae
 - Flail tricuspid valve leaflets
 - Tricuspid valve insufficiency
 - Arrhythmias or conduction disturbances
 - Premature atrial and ventricular contractions
 - Atrial flutter or fibrillation
 - Nonsustained or sustained ventricular tachycardia
 - Ventricular fibrillation
 - Bundle branch blocks
 - Heart block
 - Ventricular free wall perforation (with or without pain)
 - Pericardial effusion
 - Cardiac tamponade
 - Cardiac arrest
- Death
- Inability to obtain tissue; inadequate sample

arrest (which is rare). Vasovagal reactions can occur in the nonheart transplant population where the heart remains innervated, though it has rarely been noted in patients with orthotopic cardiac allografts if reinnervation of the graft is present. Sudden heart block can develop and may be more frequent in patients with left bundle branch block or trifascicular right bundle branch block. Pneumothorax and hemothorax are substantial risks but are lessened by using sonographic imaging of the neck and mediastinal great vessels to help guide venous access and catheter journey. Pulmonary embolization can occur, including air embolization. The operator must be ever mindful of this potential difficulty and take efforts to not allow air into the venous system, particular during deep inspiration by the patient. In the long term, perhaps one of the more problematic difficulties can be disruption of tricuspid valve integrity, particularly after repeated RV endomyocardial biopsies during follow-up of heart transplant patients. Indeed, tricuspid valve leaflets can be punctured or torn by the sheath, bioptome, chordae tendineae biopsy, or tissue removal from the tip of a papillary muscle. This can produce substantial tricuspid insufficiency. Using a long sheath that can be placed into the right ventricle across the tricuspid valve may decrease the risk of tricuspid valve trauma; however, biopsy of tricuspid valve chordae tendineae may still occur even when a sheath is used. Long sheaths might inhibit the ability to maneuver the bioptome within the ventricular chamber. The operator must be ever alert to the possibility of bleeding into the pericardium, particularly when it is vigorous enough to cause tamponade after RV free wall puncture (seemingly less likely in heart transplant patients). Fortunately, most

perforations seal off without sequelae after the culprit catheter is pulled back into the ventricle because of myocardial elasticity. However, the thin free wall of the right ventricle or areas of substantive scar tissue can produce challenges in some patients when perforation occurs. One must be vigilant after the procedure and remember that delayed complications can be seen and include access site bleeding (particularly when an artery is inadvertently punctured during the procedure or the patient is anticoagulated or taking antiplatelet agents); late cardiac tamponade; access site venous thrombosis; and, as mentioned, tricuspid insufficiency severe enough to cause hemodynamic alterations. The precise frequency of long-term adverse events, such as tricuspid regurgitation, is not well characterized.

Data are available to give insight into frequency of complications during RV endomyocardial biopsy. Overall, when large registry-based data are reviewed, the complication rate for access site acquisition is in the 2% to 3% range and with actual biopsy procedure 3% to 4% (see Table 35.1). The most recent large-scale study of endomyocardial biopsy performance and complications is that of Singh et al.³⁰ In a cohort of 71,105 adult patients (from the Healthcare Cost Utilization Project National Inpatient Sample Database) undergoing endomyocardial biopsy in the United States between 2002 and 2014, complication rates were tallied. A total of 20,770 (29%) biopsies were performed on native hearts (mean age, 52.2 ± 15.3 years; 61% men). More frequent indications for biopsy of native hearts included suspected primary cardiomyopathy, heart failure without cardiogenic shock, and acute myocarditis. Less common indications included heart failure with cardiogenic shock, unexplained heart failure with ventricular tachycardia, high-degree atrioventricular block, and cardiac neoplasms. The remaining patients were the vast majority and underwent biopsy for cardiac allograft management. Complications noted in this incredibly large dataset included pericardial effusion (3.8%), third-degree atrioventricular block (2.7%), vascular complications (1.9%), and deep vein thrombosis (DVT; 3.5%). Predictors of complications included the presence of a cardiac malignant neoplasm, use of hemodynamic support, heart failure with ventricular tachyarrhythmias, and female gender. Biopsy of a cardiac allograft was associated with lower rates of pericardial effusion, third-degree atrioventricular block, and ventricular tachyarrhythmias requiring cardioversion but higher rates of DVT, infections, and pneumothorax.

In other smaller studies, the most common complication during access site approach is unplanned arterial puncture during infusion of local anesthesia or inadvertent insertion of access catheters or bioptomes into an artery (~2%) and prolonged venous oozing after bioptome and sheath removal (<1%).³¹ Patients occasionally report sharp or pleuritic pain when specimens are removed. Despite these low numbers, it should be noted that deaths can occur after perforation of the ventricle with cardiac tamponade or development of malignant, hemodynamically unstable arrhythmias. In a large ($n = 5347$) single-center study of heart transplant and cardiomyopathy patients, death occurred in only 0.07% of patients.^{3,31} Patients having a higher risk of ventricular perforation include those

with increased RV systolic pressure, with blood clotting abnormalities, taking anticoagulants or antiplatelet agents, or having RV enlargement, which can be associated with RV wall thinning. Whenever the operator is concerned about myocardial perforation because of a pain syndrome, hypotension, or tachycardia, before central venous access is removed and the patient leaves the diagnostic laboratory, echocardiography should be performed urgently to confirm or refute the presence of pericardial fluid and document any imaging evidence of hemodynamic compromise. The capability to surgically address substantive pericardial effusions, particularly those with hemodynamic compromise from a surgical or pericardiocentesis approach, should be present and immediately available at all centers performing endomyocardial biopsy.

Many risks can be diminished by using ultrasound imaging for access site and catheter guidance, as noted, but also by avoiding the immediate supraclavicular approach with a higher internal jugular puncture technique. Rarely is heart block a permanent problem, but in patients with left bundle branch block (LBBB), when the biptome or guiding catheter is placed into the right ventricle and pressed against the intraventricular septum, LBBB can develop. Most of the time, simply pulling back on the sheath or biptome is enough to allow normal conduction to reappear, and only on rare occasions will a patient require temporary pacing. Horner syndrome with vocal paresis and sometimes diaphragmatic excursion limitation can be noted with large volume lidocaine infusion into the jugular venous and carotid sheath but does not generally result in permanent damage and resolves quickly. Trauma from the puncture needle itself can also cause this difficulty and perhaps more permanent impairment. Again, one of the troubling problems in heart transplant patients is development of tricuspid insufficiency or worsening of this problem after exposure to multiple serial biopsies.²⁴

PROCESSING ENDOMYOCARDIAL TISSUE SPECIMENS

By convention, 5 to 10 passes into the ventricle are made to obtain, generally, 5 specimens. Usually, the pieces are 1 to 2 mm in size.^{2,3} The 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology suggested “three, preferably four” fragments 1 to 2 mm in size should be obtained and then immediately fixed in a 10% buffered formalin solution and kept at room temperature to prevent contraction band formation.² In addition, one or two additional specimens should be “snap” frozen in liquid nitrogen for molecular testing or other esoteric but more specific staining procedures based on the patient’s clinical presentation. Finally, the consensus statement points out that one fragment should be fixed in a 2.5% glutaraldehyde or Karnovsky solution so that it can be used for cellular ultrastructural analysis if desired.

Pathologic examination would include light microscopy routinely performed on formalin fixed and paraffin imbedded samples with hematoxylin and eosin and a variety of

other staining techniques for more specific evaluations. This might include Masson or Mallory trichrome stain, Movat pentachrome stain, and Weigert-Van Gieson stain for collagen and elastin fibers. Periodic acid-Schiff stain with and without diastase is helpful for evaluating glycogen storage diseases, which might better be performed on frozen sections. Because amyloidosis is a frequent indication for endomyocardial biopsy, attention to Congo red sulfate, Alcian blue, or S/T thioflavin staining is important. PERLS iron stain is also useful when evaluating possible infiltrative cardiomyopathies. Histochemical, histomorphologic, and immunohistochemical stains supplement the more routine evaluation and are particularly helpful when inflammatory myocarditis or cellular infiltration is anticipated.³² Monitoring cardiac allograft patients is helped by knowledge of certain immunohistochemical reactions. These stains include CD45, 20, 3, 4, 8, 68, and HLA-DR and -ABC. Transthyretin, κ and λ chains, apolipoprotein, and amyloid A stains are helpful for amyloid typing. Certain antibodies can characterize neoplasia, and some genetic cardiomyopathies can be demonstrated with dystrophin, lamin A/C, desmin, plakoglobin, and N-cadherin in some patients. Immunohistochemical stains, including those used to type amyloid infiltration, may be performed on frozen tissue. In certain circumstances, frozen tissue appears preferable for immunohistochemistry analysis of dystrophin and HLA-ABC.

Because of the importance of myocarditis in causing acute and chronic cardiomyopathy syndromes, great attention has been played to the molecular detection of viral genomic “footprints” in the myocardium, which might suggest a specific viral attack on the heart with subsequent contractility impairment.³²⁻³⁶ Many studies have demonstrated evidence that a wide variety of viruses, including enteroviruses, adenoviruses, cytomegalovirus, herpes simplex virus, and Epstein-Barr virus, have infected the myocardium. Most frequently, adenovirus and enterovirus genomes are noted. There is a significant limitation in interpretation of viral genome data, however, because the sensitivity is not well characterized for these investigations. A positive polymerase chain reaction test result, for example, appears diagnostic but a negative examination result would not necessarily exclude a viral disease pathology. Furthermore, very small viral loads have been reported in some patients, and the clinical significance of this can be unclear. Linking viral footprint evidence of residence may not explain the etiology of a cardiomyopathy syndrome completely. The 2007 scientific statement from the AHA, the American College of Cardiology (ACC), and the ESC pointed out that because of these uncertainties, centers not experienced in techniques of viral load analysis should avoid exploration of myocardial tissue in this fashion.¹ Furthermore, the lack of consensus regarding treatment of patients with viral myocarditis, both acutely and chronically, emphasizes, arguably, the limited value today of this approach.^{22,33-36}

While performing the procedure and obtaining samples, the operator must be mindful of the fact that transmission electron microscopic examination on glutaraldehyde or Karnovsky solution-fixed specimens is important for some difficulties such as Adriamycin-induced cardiomyopathy.

Special attention needs to be paid to proper preservation of the tissue for this type of analysis. Communication between the cardiologist obtaining the specimens and the pathologist supervising sample evaluation is essential for optimizing results because much of the analysis will be driven by a patient's clinical presentation and what cardiac disorder is suspected.^{1,2}

INDICATIONS FOR ENDOMYOCARDIAL BIOPSY

Three broad categories of patients are likely to benefit from data obtained by an endomyocardial biopsy. In the first category, diagnosing a specific cause of heart failure is the leading question. After other diagnostic procedures are used and various diseases excluded, endomyocardial biopsy may provide a very specific clinical diagnosis (Table 35.2). The second category includes the necessity of making a decision regarding the importance of obtaining a definitive diagnosis, which would then dictate specific therapies (such as, arguably, for acute myocarditis) rather than nonspecific therapies (guideline-driven pharmacotherapies and electrophysiologic procedures) or clinical management (the safety of administering an anthracycline compound in an individual with recurrent malignancy treated previously with such an agent as example). The third general category is linked to the first two because of the importance of therapeutic plans being based on a clinical diagnosis. Examples include managing new onset (<~6 months) of unexplained heart failure, significant cardiac arrhythmias that might be related to myocarditis or sarcoidosis, chronic heart failure caused by hypertrophic or restrictive diseases, investigation of cardiac masses, and assessment of cardiac transplant allograft rejection. Table 35.2 summarizes the diagnostic

potential for endomyocardial biopsy, pointing out when definite, probable, and possible diagnoses can be achieved.¹⁻³

A different and clever approach was taken by the 2007 endomyocardial biopsy scientific statement from the AHA/ACC/and ESC.¹ It was much more specific with respect to the procedure's role in 14 clinical scenarios that were crafted to characterize the most common patient presentations clinicians might face while considering endomyocardial biopsy in any particular circumstance. Although now dated, this approach is still helpful and relevant. The consensus statement included the "level of recommendation" and "level of evidence" (LOE) supporting the class of recommendation. This statement used the usual AHA/ACC approach to guideline development with a Class I recommendation, meaning there is evidence or general agreement that a procedure is beneficial, useful, and effective, and a Class II indication is based on conflicting evidence or a divergence of opinion about the usefulness of a procedure and further subdivided into Class II-A in which the weight of evidence is in favor of usefulness and Class II-B in which support for a procedure's usefulness is less well established. A Class III recommendation suggests there is evidence or general agreement that a procedure is not useful and may even be harmful. Level A evidence provides the highest and least controversial data and is generally obtained from multiple randomized clinical trials. Level B evidence generally comes from limited numbers of randomized trials, nonrandomized studies, and registries, whereas the lowest LOE, Level C, has been pejoratively termed "expert opinion."

One can juxtapose the 2007, 2011, and 2021 scientific statements and see that there is relative consensus throughout the decades regarding use of endomyocardial biopsy among professional organizations.¹⁻³ The most

TABLE 35.2 Diagnostic Potential for Endomyocardial Biopsy: 2011 Consensus Statement

Definite Diagnosis can be Made
• Cardiac sarcoidosis: noncaseous granulomas • Cardiac amyloidosis: myocardial amyloid infiltration • Iron overload: intracellular iron deposition • Desmin cardiomyopathy: abnormal granulomatous aggregates of desmin-type intermediate filaments in the cytoplasm of cardiomyocytes and at the Z-band level • Dystrophin cardiomyopathy (Duchenne dystrophy): absence of dystrophin in myocyte sarcolemma • Loeffler endocarditis (acute phase)/endomyocardial fibrosis: degranulated eosinophilic endomyocardial infiltrates and endomyocardial thrombosis with evidence of endocardial fibrous thickening and subendocardial myocyte abnormalities • Cardiac tumors: cellular evidence of tumor pathology • Cardiac allografts: acute cellular rejection, antibody-mediated rejection, posttransplant lymphoproliferative disease, unusual infections (<i>Toxoplasma gondii</i>, cytomegalovirus inclusion bodies)
Probable Diagnosis can be Made
• "Toxic" myocardial disease (anthracycline) or hypersensitivity disease: eosinophilic myocarditis and myocyte degeneration with intramitochondrial inclusion bodies • Anderson-Fabry disease: hypertrophic vacuolated cells with dislocation of contractile elements to the periphery of myocytes • Mitochondrial cardiomyopathies: morphologically altered mitochondria noted on electron microscopy • Glycogen storage diseases (Pompe, Cori, Andersen, Danon diseases): diffuse intracellular glycogen deposits • Arrhythmogenic right ventricular cardiomyopathy: fibrous or fibrofatty replacement and myocardial atrophy from biopsy of the right ventricular outflow tract
Possible Diagnosis
• Hypertrophic cardiomyopathy: myocyte hypertrophy, perhaps myocyte disarray, interstitial or substitutive fibrosis • Idiopathic dilated cardiomyopathy: myocyte hypertrophy, nuclear alterations, perinuclear halo with/without fibrosis • Idiopathic restrictive cardiomyopathy: normal myocardium, fibrosis, or disarray • Laminopathies (lamin A/C): interstitial or replacement fibrosis, myocyte hypertrophy and vacuolization, enlarged and irregular-shaped nuclei

solid evidence and highest class of recommendation for using endomyocardial biopsy from the 2007 scientific statement is new onset of heart failure of less than 2 weeks' duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise, which received a Class I recommendation with LOE assigned B. This recommendation Class and LOE also was assigned to patients with new-onset heart failure (2 weeks' to 3 months' duration) associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks. Of course, when making a decision about proceeding to endomyocardial biopsy, the clinician should weigh the risks and benefits of the procedure in light of information guiding the practitioner to a definitive diagnosis, which can then influence treatment plans. Subsequent scenarios getting a II-A recommendation but rating only "expert opinion" (Class C LOE) includes patients with heart failure of longer than 3 months' duration associated with a dilated left ventricle and new ventricular arrhythmia, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks. Heart failure associated with a dilated cardiomyopathy of any duration that is seen in an individual with suspected allergic reaction or eosinophilia, heart failure associated with suspected anthracycline cardiomyopathy, heart failure with unexplained restrictive cardiomyopathy, suspected cardiac tumors, and unexplained cardiomyopathy in children fall into this recommendation class and LOE as well. A Class II-B recommendation, in which there is evidence or general agreement that endomyocardial biopsy is not useful and, in some cases, may be harmful, includes individuals with the new onset of heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block who respond to usual care within 1 to 2 weeks or heart failure of greater than 3 months' duration associated with a dilated ventricle without new ventricular arrhythmias or second- or third-degree heart block that responds to care within 1 to 2 weeks. Additionally, heart failure associated with unexplained hypertrophic cardiomyopathy, suspected arrhythmogenic RV dysplasia, and patients with unexplained ventricular arrhythmias also fall into the II-B category. A Class III recommendation, indicating there was general agreement that the procedure was not useful, was put forth for patients with unexplained atrial fibrillation. One of the obvious problems with making "clinical scenario-based recommendations" of this sort is the imprecise time course determinations that are included in the recommendation. The concept of driving decision making by a presentation of less than or more than "3 months" or "2 weeks to 3 months" seems arbitrary, however.

Giving a different perspective on the use of endomyocardial biopsy in diagnosing cardiac disease, the 2011 consensus statement lists several specific disease processes with a "definite" diagnostic potential (see [Table 35.2](#)). The majority of the diagnostic challenges occur in patients where a "definitive diagnosis" can be made but requires tissue that has pathognomonic findings of a disease that may be distributed unevenly in the myocardium and therefore prone to sampling error when biopsy specimens are obtained.

Alternatives to endomyocardial biopsy could be considered and were reviewed in the 2021 position statement. Myocarditis, amyloidosis, sarcoidosis, and cardiac allograft rejection monitoring now lend themselves to less invasive diagnostic techniques.^{3,26-29,37-40} For suspicion of early phase myocarditis (<14 days from symptoms), imaging with CMR T1-weighted protocols showing early gadolinium enhancement is suggestive of cell necrosis and fibrosis with a sensitivity and specificity of 67% and 91%, respectively. For late-phase symptom onset (>14 days), a T2-weighted imaging protocol had the greatest diagnostic accuracy (sensitivity, 71%; specificity, 72%). For amyloidosis, T1 CMR imaging of extracellular volume demonstrated sensitivity and specificity of 85% and 92%, respectively. Nuclear imaging with technetium-99 pyrophosphate-diphosphonate full-body scanning was helpful for transthyretin amyloidosis with positive uptake sensitivity and specificity each greater than 90%. And for sarcoidosis, a positive F18-fluorodeoxyglucose positron emission study suggested active inflammation and scar (sensitivity, 89%; specificity, 78%). T2-weighted CMR imaging demonstrating subendocardial, mid LV wall, inferolateral wall, or basal septum late gadolinium enhancement had a sensitivity of 93% and aspecificity of 85%. These approaches might obviate the need for endomyocardial biopsy in some patients and should be considered.

Because cardiac allograft rejection is more diffuse, endomyocardial biopsy, particularly when done serially over time, has been universally used to determine rejection severity in addition to simply making a diagnosis (see section on Endomyocardial Biopsy in Cardiac Transplant Allografts). Other pathology that can be noted on heart biopsies from cardiac allografts include posttransplant lymphoproliferative disease and some opportunistic infections that can trouble immunocompromised patients. In addition to routine tissue staining, CD4 immunohistochemical and immunofluorescence stains for antibody-mediated rejection, as opposed to lymphocytic or cell-mediated rejection, are done. Sometimes, however, severe myocardial dysfunction is noted with pathologically unremarkable endomyocardial biopsy findings, and this creates a perplexing situation.²⁴ Arguably, at the present time, serial endomyocardial biopsy in heart transplant recipients remains the best and most valued method of following these patients for allograft rejection. Alternatives, however, do include a variety of echocardiographic indices (multidimensional speckle-tracking strain), CMR T1 mapping, gene expression profiling (Molecular Microscope Diagnostic System), screening of non-HLA antibodies, and circulating donor-derived cell-free DNA as examples (Dandel).

Cardiac amyloidosis can definitively be diagnosed when amyloid infiltration plus histomorphologic findings of extracellular space expansion and collagen fiber deposition is noted. Cytoplasmic vacuolization and reduced myofibrils are also seen. Congo red, modified sulfated Alcian blue, and thioflavin-T stains are recommended when immunomicroscopy, protein sequencing, or mass spectrometry to establish the type of amyloid is required.^{2,3} See the earlier discussion of alternatives to endomyocardial biopsy to diagnose and stage amyloid heart disease.^{23,32-36} Echocardiography can give some insight into the possible presence of cardiac amyloidosis, but it is not sensitive or

specific enough to solely rely on. Unfortunately, sophisticated imaging techniques cannot be done in everyone suspected of having cardiac amyloidosis because of the frequent use of pacemakers and defibrillators in this population. More work must be done to better characterize the precise parameters to make the diagnosis, determine amyloid subtype, and allow prognostication.^{37,38}

A definitive diagnosis of cardiac sarcoidosis can be made when noncaseous granulomatous myocarditis is noted. The problem with making this diagnosis is the spotty or patchy infiltration of the heart that is characteristic of cardiac sarcoidosis. Biopsies not sampling regions infiltrated by granuloma will not allow the diagnosis to be made.²⁷ See the earlier discussion about alternative sophisticated imaging protocols to assist with making a diagnosis of cardiac sarcoidosis. Some have suggested that these protocols in conjunction with echocardiography can define areas of wall motion abnormality that should attract interest of the operator who, theoretically, can guide the bioptome into these zones.^{26,27} The reality of this occurring on a regular basis is, however, limited.

When tissue is removed in the zone of a cardiac tumor, a definite diagnosis can be made. Sometimes immunohistochemical stains can be useful for tumor typing. As with sarcoidosis, it is difficult to direct the bioptome precisely to the location of a suspected tumor. Operators should be cautioned about biopsying sessile masses in the heart because they might be thrombus formation, and there is risk of embolization. Masses having the appearance of a myxoma are generally very difficult to biopsy with currently available bioptomes.

A definitive diagnosis of desmin cardiomyopathy can be made based on ultrastructural findings, which include an abnormal granulo-filamentous aggregation of desmin-type

intermediate filaments in the cytoplasm of the cardiomyocytes and the Z-band. Electron microscopy is necessary as is immunoelectron microscopy to confirm that these aggregates are formed by desmin.

The absence of dystrophin in myocyte sarcolemma will make a definitive diagnosis of Duchenne muscular dystrophy, and the extensive irregularities and discontinuities of dystrophin in the myocyte sarcolemma provide support for a diagnosis of Becker muscular dystrophy. Immunohistochemical staining and immunofluorescent studies are required. Of course, clinical diagnoses of these syndromes are paramount.

Cardiac iron overload can be definitively determined by noting intracellular iron deposition with iron staining procedures. It is recommended that iron staining routinely be done for all endomyocardial biopsy specimens from patients with unexplained dilated cardiomyopathy undergoing this procedure.

Loeffler endocarditis can be definitively diagnosed in the acute phase when endomyocardial eosinophilic infiltration and endocardial fibrosis are noted. A possible diagnosis in the chronic phase is supported by the finding of endocardial fibrous thickening and subendocardial myocyte abnormalities. Timing of the biopsy is linked to the diagnostic probability, with biopsy utility decreasing over the course of time in this situation.

Inflammatory cardiomyopathy can be definitively diagnosed when lymphocytic, granulocytic, polymorphous, eosinophilic, necrotizing eosinophilic, giant cell, and granulomatous formation is observed with or without associated myocyte necrosis or damage.³²⁻³⁶ The diagnostic criteria and classification for myocarditis are summarized in Table 35.3. The so-called “Dallas criteria” were developed in 1986 for the Myocarditis Treatment Trial and not linked

TABLE 35.3 “Dallas” Criteria and Classification for the Pathologic Diagnosis of Myocarditis

Definition: Inflammatory infiltrate of the myocardium with necrosis or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease
Dallas Criteria and Classification
• First biopsy • Myocarditis with or without fibrosis • Borderline myocarditis • No myocarditis • Subsequent biopsy • Ongoing (persistent) myocarditis with or without fibrosis • Resolving (healing) myocarditis with or without fibrosis • Resolved (healed) myocarditis with or without fibrosis • Descriptions • Inflammatory infiltrate • Distribution: focal, confluent, diffuse • Extent: mild, moderate, severe • Type: lymphocytic, eosinophilic, granulomatous, giant cell, neutrophilic, mixed • Fibrosis • Distribution: endocardial, interstitial • Extent: mild, moderate, severe • Type: perivascular, replacement
Problems
• Substantial inter- or intraobserver variability during specimen review • Sampling error possible because of patchy infiltrates • Variance with other viral and immune activation markers • Patient outcomes not improved with therapies studied in the myocarditis treatment trial • Criteria unlikely sensitive enough to adequately identify patients with viral-mediated disease • Criteria (developed in 1986 for the myocarditis treatment trial) not linked to more sophisticated immunohistochemical studies or “viral footprint” tracking developed subsequently

to more sophisticated immunohistochemical studies or “viral footprint” tracking.⁴³⁻⁴⁵ There is substantial inter- and intraobserver variability in making the diagnosis when using the Dallas criteria. Furthermore, patients treated in the Myocarditis Treatment Trial based on endomyocardial biopsy data and this diagnostic scheme fared no better than those not getting immunosuppressive drugs. The timing of the endomyocardial biopsy in the course of the disease may have impacted diagnostic sensitivity and specificity. Still, the Dallas criteria remain in use for the diagnosis of inflammatory cardiomyopathy.

More recently, immune checkpoint inhibitors use in cancer management have increased remarkably. Cardiovascular immune-related adverse events, myocarditis in particular, have been recognized more often. Prevalence has been reported to be as high as 2.4%. Risk seems greater when these agents are combined with immunotherapy. In patients receiving checkpoint inhibitors in whom the suspicion of myocarditis arises with diagnosis usually made by CMR imaging, endomyocardial biopsy should be reserved for patients not responding to initial therapies or when the diagnosis remains in doubt.⁴⁶

Conditions in which endomyocardial biopsy can make a “probable” diagnosis include Anderson-Fabry disease, which is likely present if hypertrophic vacuolated cells with dislocation of contractile elements to the periphery of myocytes are noted. Electron microscopic study should be done to assess electron-dense concentric lamellar bodies to assist with the diagnosis.

Arrhythmogenic RV cardiomyopathy is probably present when fibrous or fibrofatty replacement and myocardial atrophy are noted in the RV outflow tract. Unfortunately, endomyocardial biopsies from the interventricular septum may not be informative because the pathologic findings tend to be in the outflow tract, which is generally a thin-walled and therefore dangerous zone to biopsy. A new electrophysiology technique has recently been touted to help with managing complex arrhythmias (as well as other cardiac diseases) and has significantly improved biopsy diagnostic yield in select patients by using electrophysiologic mapping systems coupled to intracardiac echocardiography.⁴¹

A probable diagnosis of drug-induced “toxic” myocardial disease can be seen with hypersensitivity myocarditis or findings of excessive anthracycline exposure manifest

by characteristic electron microscopic study. Indeed, electron microscopy is essential for making the diagnosis of anthracycline cardiomyopathy.

A probable diagnosis can be made of glycogen storage diseases including Pompe disease (type II glycogenoses), Cori disease (type III glycogenoses), Anderson disease (type V glycogenoses), and Dannon disease when diffuse intracellular glycogen storage abnormalities are noted. Electron microscopy and histochemical stains are useful to assess the type of intracellular deposits observed.

In mitochondrial cardiomyopathies, morphologically altered mitochondria noted on electron microscopic evaluation, often with enlarged myocytes and extensive cytoplasmic vacuolization, suggest the diagnosis of a mitochondrial cardiomyopathy.

For “laminopathies,” interstitial fibrotic replacement noted on an endomyocardial biopsy specimen accompanied by myocyte hypertrophy and vacuolization with enlarged and irregular-shaped nuclei are helpful.

“Possible” diagnoses can be made in hypertrophic cardiomyopathy when myocyte hypertrophy, interstitial fibrosis, so-called myocyte disarray, and small vessel disease can be noted. Idiopathic restrictive cardiomyopathy can be suggested when hemodynamic findings of restriction are present but the myocyte is normal in the presence of interstitial fibrosis. Making a precise diagnosis in the setting of restrictive myocardial disease can be difficult, and Table 35.4 summarizes situations when endomyocardial biopsy can provide clinical insight. Idiopathic dilated cardiomyopathy is associated with myocyte hypertrophy, nuclear alterations, perinuclear halo, and often (but not always) significant fibrosis. The findings in hypertrophic cardiomyopathy, idiopathic restrictive cardiomyopathy, and idiopathic dilated cardiomyopathy are nonspecific, and routine endomyocardial biopsy is not routinely performed in these patients.

ENDOMYOCARDIAL BIOPSY IN CARDIAC TRANSPLANT ALLOGRAFTS

In 1990, the International Society for Heart and Lung Transplantation (ISHLT) adapted a scheme for diagnosing and staging acute cell-mediated rejection after heart transplant. The most recent revision of the grading scheme done was

TABLE 35.4 Restrictive Cardiomyopathies in Which Endomyocardial Biopsy Might Provide Clinical Insight

Myocardial Disease
• Infiltrative cardiomyopathies: amyloidosis,^a fatty infiltration,^a Gaucher's disease,^a Hurler's disease, sarcoidosis^a • Noninfiltrative cardiomyopathies: diabetic, familial hypertrophic, idiopathic, pseudoxanthoma elasticum, scleroderma • Other: hemochromatosis,^a Fabry's disease, glycogen storage disease^a
Endomyocardial Disease
• Syndromes: endomyocardial fibrosis,^a hypereosinophilic syndrome,^a carcinoid heart disease, metastatic tumors,^a radiation, toxic effects of anthracycline^a • Drugs causing fibrous endocarditis: busulfan, ergotamine, mercurial agents, methysergide, serotonin

^aBiopsy can provide definite diagnosis based on 2011 Consensus Statement on Endomyocardial Biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology.

Leone O, Veinot JP, Angelini A, et al. 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. *Cardiovasc Pathol*. 2012;21:245-275.

in 2004.²⁴ A press release issued by ISHLT in 2019 noted that the current grading system had not subsequently changed, but noninvasive rejection monitoring approaches were gaining favor.⁴² Nonetheless, the ISHLT rejection staging criteria became internationally adopted by the heart transplant community, are still used today, and assist with patient management as well as investigations into immunosuppression strategies. For acute cellular rejection, when no cellular infiltration is noted, Grade 0 is assigned. Grade 1R is characterized as “mild” acute cellular rejection and is diagnosed by interstitial or perivascular inflammatory infiltrates with up to one focus of myocyte damage. Grade 2R, or “moderate,” rejection is when two or more foci of inflammatory infiltrates associated with myocyte damage are seen, with grade 3R being “severe” acute cellular rejection and reflecting diffuse inflammatory infiltrates with multifocal myocyte damage or edema, hemorrhage, and vasculitis. Antibody-mediated rejection is currently classed as grade 0 when immunohistochemical stains are negative or grade 1 when stains are positive and histologic features of myocardial capillary injury (endothelial swelling and intravascular macrophages), interstitial edema and hemorrhage, neutrophils in and around the capillaries, intravascular thrombi, and myocyte necrosis are noted. Immunofluorescence or immunoperoxidase staining for antibody-mediated rejection should include immunoglobulin stains (IgG, IgM, or IgA) and complement (C3D, C4D, or C1Q) deposition on cells and capillaries or macrophages (CD68) in capillaries and complement (C4D) deposition on capillary endothelium by immunohistochemistry.

“Nonrejection” posttransplant myocardial injury can also be noted on endomyocardial biopsy. Indeed, so-called “chronic” allograft rejection, basically small vessel atherosclerotic disease that undoubtedly reflects long-term perturbation of the immunologic situation, can cause ischemic injury. Early perioperative ischemic injury can also be noted on the first postoperative biopsy caused by cold preservation storage required during donor organ retrieval. A mixed inflammatory infiltrate of neutrophils, lymphocytes, macrophages, and eosinophils may present a challenge in distinguishing this particular process from acute cellular rejection. Late ischemic injury can be suggested by observation of small vessel arteriolar occlusion observation and substantial scarring in territories believed to be ischemic. One unusual finding has been called the “Quilty” effect, named after the first heart transplant patient at Stanford University with this finding.²⁴ The effect is an intense focus of endocardial infiltrate that has a nodular quality extending some into the underlying myocardium with or without significant myocyte damage. This endocardial infiltrate often is associated with prominent vascularity and an intense lymphocytic beehive appearance. The relationship of the Quilty effect to substantial pathologic difficulties, if any, after heart transplant is not clear.

EXPERT PRACTICE SUMMARY

Endomyocardial biopsy can be a valuable diagnostic procedure, although biopsy can cause egregious complications and even, though rare, death. Its utility focuses

on the evaluation of myocardial tissue, particularly for monitoring patients after cardiac transplantation (the indication for the vast majority of these procedures). In the proper setting, endomyocardial biopsy assists with making a diagnosis of inflammatory heart disease, cardiac drug toxicity, unexplained or cryptogenic cardiomyopathies, certain arrhythmias, secondary myocardial involvement in systemic diseases, or cardiac masses or myocardial tumor infiltration. Many disease states can be definitively diagnosed, particularly cardiac allograft rejection, myocarditis, and some infiltrative as well as “myocardial storage” diseases. Because of the focal nature of some diseases such as sarcoidosis, it is less helpful when biopsy findings pathognomonic of the disease are absent. To best manage patients with amyloidosis, hemochromatosis, Anderson-Fabry disease, and myocarditis, endomyocardial biopsy information may be essential. However, multimodal cardiac imaging is gaining greater respect with regard to diagnosing several difficulties. Still, some believe that having tissue for pathologic evaluation seems preferable. [Table 35.5](#) summarizes data from a creative clinical study that examines the clinical utility of endomyocardial biopsy by relating the number of biopsies that were pathologically diagnostic and altered management strategies in 851 nonheart transplant patients who were categorized according to the 14 clinical scenarios outlined in the ACC/AHA scientific statement regarding the role of endomyocardial biopsy.²⁶ The study confirmed the fact that the procedure was generally safe and overall provided a specific diagnosis and influenced alteration in medical management plans about 26% of the time. Diagnostic success rates ranged from 0% (in unexplained atrial fibrillation patients) to 50% (in patients with suspected anthracycline toxicity), and the range for biopsy result-driven alteration of medical management was 11% (new onset of dilated cardiomyopathy without arrhythmia) to 38% (again in suspected anthracycline toxicity patients). A study of this nature needs to be repeated so that a contemporaneous insight can be gained and, in particular, compared with the newer noninvasive approaches often being turned to presently.

CONCLUSIONS

Although endomyocardial biopsy procedures have evolved dramatically over time and, relatively speaking, are safe, major complications and rarely death can occur during or shortly after the procedure. Long-term adverse sequelae of repeated biopsies, particularly in patients after heart transplantation, are noted, and operators must be sensitive to this fact, particularly the clinical scenario of deteriorating RV function in a setting of substantive tricuspid valve insufficiency. Endomyocardial biopsy is not a procedure “looking for an indication,” but wisdom must guide its application and performance in carefully selected patients and be done by experienced operators having adequate infrastructure for procedure performance and, equally important, tissue evaluation.

TABLE 35.5 Diagnostic Yield and “Clinical Utility” of Endomyocardial Biopsies in 851 Nonheart Transplant Patient Scenarios

CLINICAL SCENARIO	BIOPSY DIAGNOSTIC (%)	BIOPSY-ALTERED MANAGEMENT (%)
Suspected anthracycline toxicity (n = 24)	50	38
Acute HF with HYD compromise (n = 109)	39	28
DCM with “allergic reaction” suspected (n = 9)	33	33
“Restrictive” CM (n = 286)	29	26
Unexplained HCM (n = 28)	25	29
Unexplained ventricular arrhythmia (n = 8)	25	13
Suspected ARVD (n = 62)	24	39
Suspected cardiac tumor (n = 4)	25	25
New DCM, arrhythmia, poor response (n = 29)	21	28
Chronic DCM, arrhythmia, poor response (n = 26)	19	12
Unexplained pediatric CM (n = 29)	17	26
Stable chronic DCM, no arrhythmia (n = 134)	16	13
New-onset DCM, no arrhythmia (n = 100)	14	11
Unexplained AF (n = 3)	0	
OVERALL (851 total cases)	26	26

AF, Atrial fibrillation; ARVD, arrhythmogenic right ventricular dysplasia; CM, cardiomyopathy; DCM, dilated cardiomyopathy; HF, heart failure; HYD, hemodynamic compromise. Modified from Bennett MK, Gilotra NA, Harrington C, et al. Evaluation of endomyocardial biopsy in 851 patients with unexplained heart failure from 2000-2009. *Circ Heart Failure*. 2013;6:676-684.

REFERENCES

- Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology endorsed by Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J*. 2007;28(24):3076-3093.
- Leone O, Veinet JP, Angelini A, et al. 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. *Cardiovasc Pathol*. 2012;21:245-274.
- Seferovic PM, Tsutsui H, McNamara DM, et al. Heart Failure Association, Heart Failure Society of America, Japanese Heart Failure Society position statement on endomyocardial biopsy. *J Card Fail*. 2021;27(7):727-743.
- Melvin KR, Mason JW. Endomyocardial biopsy: its history, techniques and current indications. *Can Med Assoc J*. 1982;126:1381-1386.
- Brock R, Milstein BB, Ross DN. Percutaneous left ventricular puncture in the assessment of aortic stenosis. *Arch Surg*. 1958;76:825-829.
- Menezes MN, Oliveira EI, Silva ACE, et al. Traditional left ventricular endomyocardial biopsy feasibility, safety, and clinical usefulness: initial experience of a tertiary university center. *Rev Port Cardiol*. 2020;39(8):453-460.
- Weinberg M, Fell EH, Lynfield J. Diagnostic biopsy of the pericardium and myocardium. *AMA Arch Surg*. 1958;76:825-829.
- Sutton DC, Sutton GC, Kent G. Needle biopsy of the human ventricular myocardium. *Q Bull Northwest Univ Med Sch*. 1969;30:212.
- Burger H, Richter M, Classen K, et al. Transvenous endomyocardial biopsy: a comparison of 2 approaches. *Transplant Proc*. 2021;53:324-328.
- Sakakibara S, Konno S. Endomyocardial biopsy. *Jpn Heart J*. 1962;3:537-543.
- Konno S, Sekiguchi M, Sakakibara S. Catheter biopsy of the heart. *Radiol Clin North Am*. 1971;9:491-510.
- Caves PK, Stinson EB, Billingham M, et al. Percutaneous transvenous endomyocardial biopsy in human heart recipients. *Ann Thorac Surg*. 1973;16:325-336.
- Mackay EH, Littler WA, Sleight P. Critical assessment of diagnostic value of endomyocardial biopsy. *Br Heart J*. 1978;40:69-78.
- Shirey EK, Proudfoot WL, Hawk WA. Primary myocardial disease: correlation with clinical findings, angiographic and biopsy diagnosis. *Am Heart J*. 1980;99:198-207.
- Scholten Surgical Instruments, Inc. Available at: <https://novatome.com>.
- Richardson PJ. King's endomyocardial biopome. *Lancet*. 1974;303:660-661.
- Fowler NO. Classification and differential diagnosis of the myocardopathies. *Prog Cardiovasc Dis*. 1964;7:1-16.
- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:e240-e327.
- Leone O, Veinot JP, Angelini A, et al. 2011 Consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. *Cardiovasc Pathol*. 2012;21:245-275.
- Keenan SP. Use of ultrasound to place central lines. *J Crit Care*. 2002;17:126-137.
- Miller LW, Labovitz AJ, McBride LA, et al. Echocardiography-guided endomyocardial biopsy: a 5-year experience. *Circulation*. 1988;78(Pt 2):III99-III104.
- Jang SY, Cho Y, Song JH, et al. Complication rate of transfemoral endomyocardial biopsy with fluoroscopic and two-dimensional echocardiographic guidance: a 10-year experience of 228 consecutive procedures. *J Korean Med Sci*. 2013;28:1323-1328.
- Aaron M, Maleszewski JJ, Rihal CS. Current status of endomyocardial biopsy. *Mayo Clin Proc*. 2011;86:1095-1102.
- Writing Committee for the International Society of Heart and Lung Transplantation. Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. 2010;29:914-956.
- Chimenti C, Frustaci A. Contribution and risks of left ventricular endomyocardial biopsy in patients with cardiomyopathies. *Circulation*. 2013;128:1531-1541.
- Bennett MK, Gilotra NA, Harrington C, et al. Evaluation of endomyocardial biopsy in 851 patients with unexplained heart failure from 2000-2009. *Circ Heart Fail*. 2013;6:676-684.
- Patel MR, Cawley PJ, Heitner JF, et al. Detection of myocardial damage in patients with sarcoidosis. *Circulation*. 2009;120:1969-1977.
- Blankstein R, Osborne M, Naya M, et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. *J Am Coll Cardiol*. 2014;63:329-336.
- Aljaroudi WA, Desai MY, Tang WH, et al. Role of imaging in the diagnosis and management of patients with cardiac amyloidosis: state of the art review and focus on emerging nuclear techniques. *J Nucl Cardiol*. 2014;21:271-283.
- Singh V, Mendirichaga R, Savani GT, et al. Comparison of utilization trends, indications, and complications of endomyocardial biopsy in native versus donor hearts (from a nationwide inpatient sample 2002 to 2014). *Am J Cardiol*. 2018;121:356-363.
- Fiorelli AL, Benvenuti L, Aiello V, et al. Comparative analysis of the complications of 5347 endomyocardial biopsies applied to patients after heart transplantation and with cardiomyopathies: a single center study. *Transplant Proc*. 2012;44:2473-2478.
- Basso C, Calabrese F, Angelini A, et al. Classification and immunohistochemical, and molecular diagnosis of inflammatory myocardial disease. *Heart Fail Rev*. 2013;18:673-681.
- Kindermann I, Barth C, Mahford F, et al. Update on myocarditis. *J Am Coll Cardiol*. 2012;59:779-792.
- Mason JW. Basic research on myocarditis. *J Am Coll Cardiol*. 2013;19:1746-1747.
- Hazebroek MR, Everaerts K, Heymans S. Diagnostic approach of myocarditis: strike the golden mean. *Neth Heart J*. 2014;22:80-84.
- Baughman KL. Diagnosis of myocarditis: death of the Dallas criteria. *Circulation*. 2006;113:593-595.
- Dungu JN, Valencia O, Pinney JH, et al. CMR-based differentiation of AL and ATTR cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2014;7:133-142.
- White JA, Kim HW, Shah D, et al. CMR imaging with rapid visual T1 assessment predicts mortality in patients suspected of cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2014;7:143-156.

39. Fontana M, Banypersad SM, Treibel TA, et al. Native T1 mapping in transthyretin amyloidosis. *JACC Cardiovasc Imaging*. 2014;7:157-165.
40. Kwong RY, Jerosch-Herold M. CMR and amyloid cardiomyopathy: are we getting closer to the biology? *JACC Cardiovasc Imaging*. 2014;7:166-168.
41. Casella M, Dello Russo A, Vettor G, et al. Electroanatomical mapping systems and intracardiac echo integration for guided endomyocardial biopsy. *Expert Rev Med Devices*. 2017;14(8):609-619.
42. International Society for Heart and Lung Transplantation. *New Approach to Assessing Rejection in Heart Transplant Patients Far More Effective*. Available at: https://ishlt.org/ishlt/media/Documents/ISHLT2019_Potena_PressRelease.pdf.
43. Dandel M, Hertz R. Non-invasive cardiac allograft rejection surveillance: reliability and clinical value for prevention of heart failure. *Heart Failure Rev*. 2021;26(2):319-336.
44. Hahn EA, Hartz VL, Moon TE, et al. The myocarditis treatment trial: design, methods and patient enrollment. *Eur Heart J*. 1995;16(suppl O):162-167.
45. Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. *N Engl J Med*. 1995;333:269-275.
46. Ball S, Ghosh RK, Wongsasengsak S, et al. Cardiovascular toxicities of immune checkpoint inhibitors. *J Am Coll Cardiol*. 2019;74:1714-1727.



INTRODUCTION, 663

THE NORMAL PERICARDIUM, 663

PERICARDIAL EFFUSION AND
TAMPONADE, 664CLINICAL DIAGNOSIS OF PERICARDIAL
TAMPONADE, 664INDICATIONS FOR
PERICARDIOCENTESIS, 665

PERICARDIOCENTESIS TECHNIQUE, 665

POSTPERICARDIOCENTESIS CATHETER
MANAGEMENT, 666COMPLICATIONS OF
PERICARDIOCENTESIS, 667MALIGNANT, RECURRENT, OR
PERSISTENTLY DRAINING PERICARDIAL
EFFUSIONS, 667TECHNIQUE OF SINGLE-BALLOON
PERCUTANEOUS BALLOON
PERICARDIOTOMY, 668TECHNIQUE OF DOUBLE-BALLOON
PERCUTANEOUS BALLOON
PERICARDIOTOMY, 669OUTCOMES AFTER PERCUTANEOUS
BALLOON PERICARDIOTOMY, 670PERCUTANEOUS PERICARDIAL
BIOPSY, 670TECHNIQUE OF PERCUTANEOUS
PERICARDIAL BIOPSY, 671

ROLE OF PERICARDIOSCOPY, 672

PERCUTANEOUS EPICARDIAL ACCESS
FOR ELECTROPHYSIOLOGY STUDIES AND
ABLATION, 672TECHNIQUE OF PERICARDIAL ACCESS
AND EPICARDIAL MAPPING AND
ABLATION, 672LIMITATIONS AND POTENTIAL
COMPLICATIONS OF PERICARDIAL ACCESS
AND EPICARDIAL ABLATION, 673PERCUTANEOUS PERICARDIAL ACCESS
FOR TRANSCATHETER LEFT ATRIAL
APPENDAGE LIGATION, 673

PREPROCEDURAL CONSIDERATIONS, 674

TECHNIQUE OF PERCUTANEOUS
TRANSPERICARDIAL LEFT ATRIAL
APPENDAGE EXCLUSION, 675

PROCEDURAL COMPLICATIONS, 677

FUTURE PERSPECTIVES, 677

INTRODUCTION

Pericardial disease has a wide range of clinical presentations and pathologies, from acute pericarditis to cardiac tamponade. Unlike coronary artery disease, heart failure, or valvular heart disease, however, there are few randomized clinical trial data to guide physicians and interventionalists in management. There are currently no American College of Cardiology guidelines on management of pericardial disease, with only European Society of Cardiology guidelines available to aid in the diagnosis and management of these conditions.¹

The clinical presentation of pericardial effusions are variable; some are completely asymptomatic, and others can present with cardiac tamponade and hemodynamic collapse.^{2,4} Pericardiocentesis is a catheter-based technique using a needle to aspirate the pericardial fluid, usually under electrocardiographic (ECG), fluoroscopic, or echocardiographic guidance. Percutaneous balloon pericardiotomy (PBP) is a relatively novel catheter-based technique offering a less invasive technique than conventional surgical pericardial window to treat recurrent pericardial effusions or malignant effusions. Improvements in the access technique to the pericardial space and the concomitant use of pericardioscopy have led to the development of a number of novel interventional techniques over the past 3 decades; from percutaneous biopsy of the pericardium to epicardial electrophysiological ablation procedures and, more recently, percutaneous ligation of

the left atrial appendage (LAA) as a method of stroke prevention in individuals with permanent atrial fibrillation (AF) in whom anticoagulation is contraindicated.

These pericardial techniques, their indications and supporting clinical evidence, and procedural complications are discussed in detail in this chapter.

THE NORMAL PERICARDIUM

The pericardium is a relatively avascular fibroelastic sac that surrounds the heart composed of two layers, a visceral and parietal layer, separated by a potential space containing 15 to 35 mL of straw-colored serous fluid.³ The visceral pericardium is composed of a single layer of mesothelial cells adherent to the myocardial surface. The parietal pericardium is a fibrous structure composed primarily of collagen and a lesser amount of elastin.

As a result of its fibrous inelastic qualities, the normal pericardium has a relatively steep pressure-volume curve. It is distensible when the intrapericardial volume is small but becomes gradually inextensible when the volume increases. In the presence of a pericardial effusion, the intrapericardial pressure depends on the relationship between the absolute volume of the effusion, the speed of accumulation of the fluid, and the intrinsic pericardial elasticity. Therefore, the clinical presentation of pericardial effusion depends not only on the volume of the effusion but also on the rapidity of fluid accumulation.^{5,6}

PERICARDIAL EFFUSION AND TAMPONADE

Pericardial effusion may result from a variety of clinical conditions (Table 36.1). Transudative fluids result from obstruction of fluid drainage through lymphatic channels. Exudative fluids occur secondary to inflammatory, infectious, malignant, or autoimmune processes. The frequency of specific causes varies greatly based on geography. In developed countries, both malignancy and infection are the most common causes of pericardial effusion. A pericardial effusion is associated with a known systemic disease in approximately 60% of cases.⁷⁻⁹

Pericardial effusions may be asymptomatic or manifest a wide range of clinical symptoms. Patients can report pericarditis-related chest pain, which is typically relieved by sitting up and worsened by lying supine and deep breathing. They may report palpitations most frequently caused by atrial arrhythmias. They may manifest generalized symptoms such as dyspnea and cough, presyncope or syncope, dysphagia, abdominal fullness, anxiety, cyanosis, and fever. Large pericardial effusions in the absence of inflammatory signs and symptoms are often neoplastic.¹⁰

Cardiac tamponade is a life-threatening condition that results from the accumulation of intrapericardial fluid that impairs ventricular diastolic filling.⁶ Ultimately, cardiac chambers are compressed and fail to fill when their pressures are exceeded by the intrapericardial pressure. Because of their lower pressures, the right heart chambers are more prone to compression. The intrapericardial pressure depends on the volume of the effusion, the speed of accumulation, and the pericardial elasticity.¹¹ Rapidly accumulating effusions result in cardiac tamponade at relatively small volumes because the pericardium does not have adequate time to stretch. When effusions accumulate slowly, pericardial compliance gradually increases, allowing the pericardium to accommodate large volumes (as much as 2–3 L). Malignancy is the most common cause of pericardial effusion with tamponade (~50%).

In all cases of cardiac tamponade, the initial treatment consists of removing pericardial fluid by prompt pericardiocentesis and drainage.⁸ Reaccumulation is common, especially in malignant effusions, and is traditionally an indication for surgical pericardial window. Autopsy and surgical studies have demonstrated myocardial or pericardial metastatic deposits in approximately 50% of patients presenting with malignant effusion related cardiac tamponade. Although the short-term survival of patients with tamponade depends on its early diagnosis and prompt treatment, long-term survival is dictated by the prognosis of the underlying primary illness, regardless of the surgical technique or interventional procedure performed.^{7,12}

CLINICAL DIAGNOSIS OF PERICARDIAL TAMPONADE

Clinical findings suggestive of pericardial tamponade include:

- Beck's triad of tamponade: hypotension, distant heart sounds, and jugular venous distension
- Pulsus paradoxus: a decrease in systolic blood pressure of more than 10 mm Hg with inspiration caused by a reduction in cardiac output during inspiration. With inspiration, negative intrathoracic pressures increase venous return and filling of the right-sided chambers. The interventricular septum consequently bows to the left, reducing left ventricular filling and output. This is quantified during the physical examination using a manual sphygmomanometer cuff during normal respirations by listening for Korotkoff sounds. As the cuff pressure is slowly reduced, Korotkoff sounds will initially be intermittent and become continuous with further reduction in the cuff pressure. The difference in the pressure measurement at which Korotkoff sounds are first audible and become continuous defines the pulsus.
- Elevated jugular venous pressure with loss of the Y descent of the jugular venous pulse

TABLE 36.1 Causes of Pericardial Effusion

INFECTIOUS	NEOPLASTIC	INFLAMMATORY	METABOLIC AND MISCELLANEOUS
Viral: coxsackievirus, echovirus, cytomegalovirus, Epstein-Barr virus, herpes, varicella, hepatitis	Primary: mesothelioma; fibrosarcoma	Acute rheumatic fever	Idiopathic
Bacterial: tuberculosis, staphylococcus, streptococcus, gram-negative bacteria, gonococcus, rickettsia	Metastatic: lung cancer, melanoma, breast cancer, lymphoma, leukemia	Rheumatoid arthritis	Myxedema
Fungal: <i>Histoplasma</i> spp., <i>coccidioides</i> spp., <i>Candida</i> spp., <i>Aspergillus</i> spp., <i>Blastomyces</i> spp., <i>Actinomyces</i> spp.		Systemic lupus erythematosus	Uremia
Parasitic infection: <i>Entamoeba</i> spp., echinococcosis, toxoplasmosis, trypanosomiasis		Systemic sclerosis	Adverse drug reactions
		Still's disease	Radiation
		Dressler's syndrome	Traumatic
		Other vasculitides	Aortic dissection
		Mixed connective tissue disease	Post cardiac surgery
			Chylopericardium
			Myocardial Infarction

A pericardial friction rub is associated with acute pericarditis and can occur with effusions. This high-pitched scratching sound is best auscultated at the left lower sternal border with the patient leaning forward. A rub typically consists of three components, namely, ventricular systole, ventricular diastole, and atrial systole. Frequently, only one or two of the components are audible. Additionally, the patient may demonstrate tachycardia and tachypnea and have signs of venous congestion with ascites, hepatosplenomegaly and lower extremity edema.⁸

On the ECG, pericarditis with an effusion may produce the following typical ECG changes:

- Widespread ST-segment elevation (>25% of the height of the T wave)
- PR depression (elevation is often seen in lead aVR)
- Low voltage, which can be indicative of a large pericardial effusion
- Electrical alternans, which may result as the heart swings within a large pericardial effusion

INDICATIONS FOR PERICARDIOCENTESIS

Pericardiocentesis is the technique of catheter-based aspiration and drainage of pericardial fluid. It may serve both as a diagnostic and potentially therapeutic procedure in patients with pericarditis with pericardial effusion, chronic pericardial effusion, effusive-constrictive pericardial effusion, and pericardial effusion with cardiac tamponade.

Many asymptomatic large pericardial effusions do not require pericardiocentesis by themselves if they do not produce hemodynamic compromise unless there is a need to perform fluid analysis to aid diagnosis. The yield of pericardial fluid analysis in determining the cause of pericardial effusion is low. Prospective long-term follow-up of patients with large idiopathic chronic pericardial effusions has demonstrated that these effusions can be well tolerated for long periods in the majority of cases; however, the risk of developing tamponade is unpredictable. Although pericardiocentesis may be effective at draining the fluid collection, it frequently reaccumulates. Therefore, in this situation, it is recommended that the patients be considered for early definitive pericardiotomy or pericardial window creation.^{10,13,14}

In patients with pretamponade or overt cardiac tamponade, emergency drainage of pericardial fluid is a life-saving therapy, avoiding hemodynamic collapse and cardiac arrest with pulseless electrical activity. In situations of impending circulatory collapse or overt tamponade, pericardiocentesis can be performed blindly using anatomic landmarks, but in more stable circumstances, it is advisable to use ECG, echocardiographic, and fluoroscopic guidance.^{3,15}

When performing pericardiocentesis, several objectives should be achieved:

1. Relief of tamponade, if present
2. Obtaining fluid for appropriate diagnostic analysis
3. Assessment of pericardial and right heart hemodynamics before and after fluid drainage to assess for effusive-constrictive pericarditis

Elective pericardiocentesis is contraindicated in patients receiving systemic anticoagulation, patients with platelet or

bleeding disorders, patients with a platelet count of less than 50,000/ μ L, and suspected hemorrhagic pericardial effusion from acute aortic dissection. Additionally, pericardiocentesis should be performed with caution in persons with organized or loculated pericardial effusions or significant pericardial adhesions from prior surgery. Consideration in these cases should be given to surgical pericardiotomy or pericardioscopic-assisted pericardial access.

PERICARDIOCENTESIS TECHNIQUE

Pericardiocentesis is most often performed within the catheterization laboratory under fluoroscopic and ECG guidance. However, the procedure can also be safely performed at the bedside under echocardiographic guidance.¹⁵

The most common approach is subxiphoid, although apical and parasternal approaches are also feasible. The subxiphoid is the safest approach when echocardiographic guidance is not available.

The skin in the subxiphoid area is shaved and sterilized with a topical antiseptic solution. The patient is then draped with an aperture drape sheet. The patient is placed on continuous cardiac and blood pressure monitoring. Prophylactic broad-spectrum antimicrobial antibiotics should be administered using a single intravenous dose of a second- or third-generation cephalosporin antibiotic or vancomycin if the patient has a penicillin allergy or is colonized with methicillin-resistant *Staphylococcus aureus* (MRSA).

An ECG electrode is attached to a large-bore needle at least 5 cm in length using an alligator clip. Most operators use either a Tuohy spinal needle or Pajunk needle for pericardial access, although increasingly operators prefer to access using a 4-Fr micropuncture needle kit to minimize injury if the puncture is performed in the wrong location. Pericardiocentesis uses the Seldinger technique of catheter insertion.

After administration of local anesthesia, the needle is slowly advanced toward the pericardial space. For the subxiphoid approach, the needle is inserted in the angle between the xiphoid process and the left costal margin and advanced at a 45-degree angle toward the left shoulder. For the apical approach, echocardiography is often used to identify the spot at this the pericardium is closest to the skin. Alternatively, the needle is inserted 1 cm outside the point of maximal impulse within the intercostal space and directed toward the right shoulder. For the parasternal approach, the needle is inserted immediately adjacent to the sternum, usually in the fifth intercostal space, with care being taken to avoid the vessels coursing along the inferior border of each rib.

Regardless of approach, the needle is slowly advanced with periodic attempts to gently aspirate fluid. While the needle is advanced, special attention is given to the attached ECG electrode lead. Elevation of the ST or PR segment is seen when the needle is in direct contact with the myocardium. Atrial or ventricular ectopic beats can also be seen. If this occurs, slow withdrawal of the needle until ECG changes resolve should position the needle tip within the pericardial space.

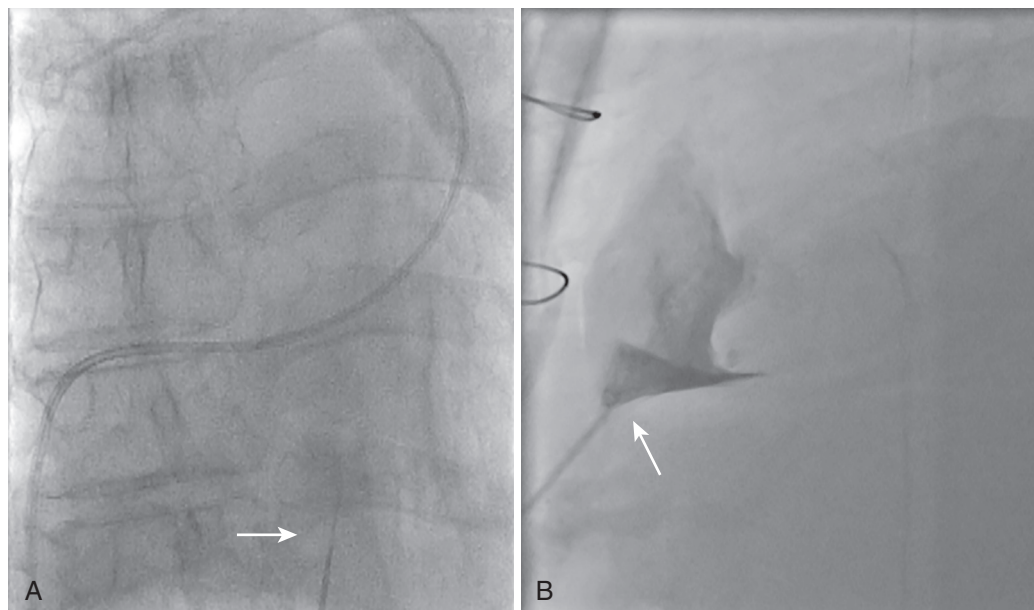


FIGURE 36.1 Subxiphoid needle access for pericardiocentesis. Anteroposterior (A) and lateral (B) projections of needle access to the pericardial space. Contrast injection through the access needle can be used to confirm successful pericardial space access on fluoroscopy (arrows). Alternatively, agitated saline can be injected and visualized on echocardiography.

A discrete pop is often felt upon entering the pericardial space. After the pericardial space is entered, contrast or agitated saline injection can confirm needle position using either fluoroscopy or echocardiography, respectively (Figure 36.1 and Video 36.1). This is especially recommended if hemorrhagic fluid is obtained. Alternatively, the aspirate can be placed injected into a cup. Pericardial fluid, even when hemorrhagic, will not clot, but intracardiac blood will.

A stiff 0.035-inch guidewire is introduced into the pericardial space through the needle. A dilator is used to dilate the soft tissue tract, and a pigtail pericardial drainage catheter is then inserted over the stiff guidewire (Figure 36.2). In the catheterization laboratory, the intrapericardial pressures should then be documented by transducing the pericardial catheter. Additionally, radiographic contrast material can be injected through the catheter to confirm position and freedom within the pericardial space.

The pericardial fluid is then drained. Table 36.2 outlines the basic biochemical, microbiologic, and pathologic analysis pericardial fluid should be tested for. When this is complete, pericardial pressures are often reassessed to document the degree of improvement. The pericardial catheter is often left in place to allow for continuous drainage or as a route to allow percutaneous pericardial window creation or instillation of sclerosing or chemotherapeutic agents. In this situation, the catheter is sutured in place, and a sterile dressing is applied.

Echocardiographic guided pericardiocentesis is a safe and effective alternative to conventional ECG and fluoroscopic guidance. In a case series of 1127 therapeutic echocardiography-guided pericardiocentesis procedures performed in 977 patients at the Mayo Clinic from 1979 to 1998, the procedural success rate was 97%, with an overall complication rate of 4.7%. Echocardiography guidance is particularly useful in organized loculated effusions and

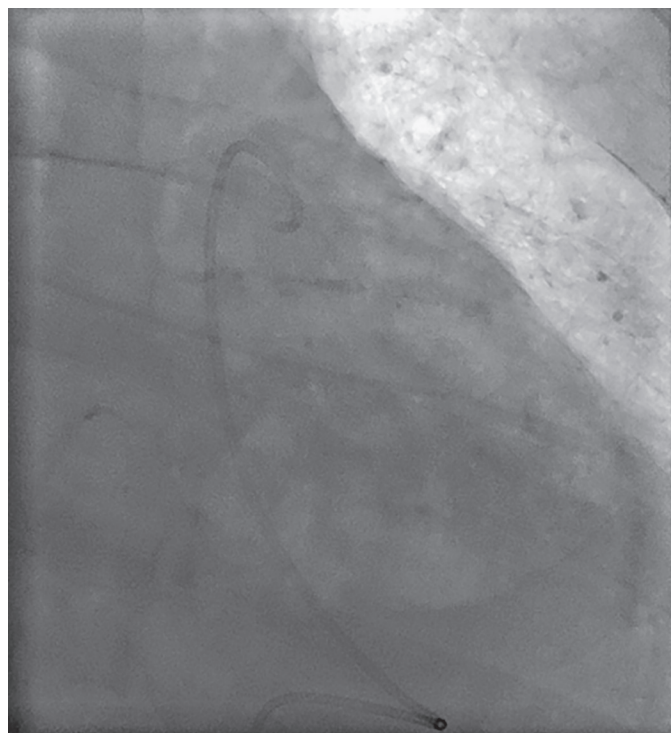


FIGURE 36.2 Successful placement of a pigtail pericardial drainage catheter.

often uses a left anterior chest wall approach rather than the conventional subxiphoid approach.³

POSTPERICARDIOCENTESIS CATHETER MANAGEMENT

Pericardiocentesis may not completely remove the effusion in most cases; therefore, it is not unusual for the

TABLE 36.2 Pericardial Fluid Analysis: Typical Biochemical, Microbiologic, and Pathologic Testing of Pericardial Fluid

BIOCHEMISTRY	EXUDATIVE EFFUSION IS CHARACTERIZED BY:	MICROBIOLOGY	PATHOLOGY	SPECIALIZED TEST
Total protein	Total protein fluid:serum >0.5	Gram stain	Fluid cytology	Viral PCR
Glucose	LDH: fluid:serum >0.6 r LDH >300 U/dL	Aerobic and anaerobic cultures	Fluid immunohistochemistry	TB PCR
Specific gravity	LDH fluid level >two-thirds the upper-limit of normal serum level	Acid-fast bacilli staining		Adenosine deaminase
LDH	Glucose: fluid:serum <1	Tuberculous cultures		Tumor markers
Fluid hematocrit	Specific gravity >1.015	Viral cultures		
Cell count	Total protein >3.0 mg/dL			

LDH, Lactate dehydrogenase; PCR, polymerase chain reaction; TB, Tuberculosis.

drainage catheter to be kept in place for 24 to 72 hours after the procedure.

Attempts to drain the pericardium should continue until less than 50 cc of fluid is drained within a 24-hour period. However, the catheter should be removed as soon as possible to minimize the risk of infection within the pericardial space.

The patient is usually maintained on continuous cardiac monitoring, and the volume and rate of catheter drainage are recorded. The pericardial catheter can be drained by gravity continuously or alternatively drained manually using sterile technique every 4 to 8 hours. Heparinized saline (2–3 cc) should be instilled into the catheter after each drainage attempt. Follow-up echocardiography can be useful to determine resolution of the collection. Intravenous antibiotics are given while the drain remains in place for prophylaxis against pericardial infection. It is our institutional practice to administer cefotaxime 1 g every 8 hours or vancomycin 500 to 1000 mg every 12 hours if the patient has a penicillin allergy or MRSA colonization.

Patients who continue to drain more than 75 to 100 mL daily 3 days after catheter placement or who reaccumulate with recurrence of tamponade should be considered for additional therapeutic strategies, including intrapericardial sclerosing or chemotherapy agents, radiotherapy, percutaneous balloon pericardial window (as outlined below), and surgical pericardial window.

COMPLICATIONS OF PERICARDIOCENTESIS

Although pericardiocentesis can be performed safely, there is the potential to traumatize surrounding structures, perforate cardiac chambers, and lacerate coronary arteries or veins.

Most often, cardiac perforation involves the right ventricle when using the subxiphoid approach for pericardiocentesis. Bleeding from a right ventricular (RV) puncture is often not severe because of the chamber's relatively low pressures. However, the thin RV wall is vulnerable to laceration, which frequently leads to substantial bleeding. This is especially possible in patients with pulmonary arterial hypertension and RV dysfunction.

Ectopic atrial or ventricular beats may occur when the pericardiocentesis needle is in direct contact or perforates

the myocardium. Sustained arrhythmias are also possible but less common.

Coronary arterial injury or spasm can occur also. The right coronary artery is most frequently perforated or lacerated during the subxiphoid approach. The left anterior descending artery and its branches can similarly be injured during apical pericardiocentesis. The internal mammary artery and inferior phrenic arteries are prone to injury during the parasternal and subxiphoid approaches, respectively.

Acute pulmonary edema can occur rarely when the pericardial effusion is decompressed too rapidly. Pneumothorax from puncture of the left pleura and lingula has also been described. Pneumopericardium can occur from introduction of air at the time of catheter placement. Additionally, it may be possible to cause a systemic air embolism if air is introduced into a cardiac chamber inadvertently. Injury to intercostal, internal mammary, or phrenic arteries may result in hemothorax. Needle perforations of the inferior vena cava, liver, stomach, and colon have all been described.

MALIGNANT, RECURRENT, OR PERSISTENTLY DRAINING PERICARDIAL EFFUSIONS

The management of chronic or recurrent pericardial effusions represents a challenge for both interventional cardiologists and cardiac surgeons because of the general moribund state of patients with this condition. In the developed world, chronic or recurrent pericardial effusions are most likely malignant (25%–50% of cases depending on case series) or infectious (27%).^{7,10,16}

Cancers that commonly cause malignant pericardial effusions in decreasing frequency include lung carcinoma, breast carcinoma, lymphoma or leukemia, pancreatic carcinoma, ovarian carcinoma, carcinoma of unknown primary, and melanoma. Primary pericardial tumors such as fibrosarcomas or mesotheliomas are rare.

Autopsy series of patients with a preexisting diagnosis of malignancy demonstrate pericardial metastatic involvement in up to 15% to 30%. However, only about 20% of patients with malignant pericardial disease present with effusion, and in up to two-thirds, the pericardial effusion can be caused by other nonmalignant mechanisms.

Malignancy can result in pericardial effusion by a number of mechanisms, including direct invasion, metastasis from distant primary cancers, lymphatic obstruction, chemotherapeutic or radiation-induced toxicities (e.g., cyclophosphamide-induced myopericarditis or radiation-induced effusive-constrictive pericarditis), or opportunistic infection from chemotherapy-induced immunosuppression (e.g., tuberculous, fungal or cytomegalovirus pericarditis).

After catheter drainage as described earlier, malignancy-related pericardial effusion reaccumulates in 15% to 50% of cases. Additionally, malignant effusions recur in approximately 5% of patients after surgical subxiphoid pericardial windowing. Neither treatment has been demonstrated to reduce mortality rates (which is determined by the underlying malignancy).^{10,12,17}

Persistent pericardial drainage is defined as more than 100 mL per 24-hour day drainage 3 days after pericardial catheter placement. Guidelines recommend more aggressive therapy for patients with persistent drainage or reaccumulation, including chemotherapeutic or sclerosant agents, PBP, or surgical pericardiectomy (level of evidence [LOE] B; Class of recommendation IIb).¹

Systemic chemotherapy or radiation therapy after catheter drainage has been shown to prevent reaccumulation in malignant effusions, reducing reaccumulation rates to approximately 30% to 40%.

Intrapericardial chemotherapeutic or sclerosant agents have also been used. A number of agents have been used, including tetracyclines, bleomycin, cisplatin, nitrogen mustard, fluorouracil, teniposide, and thiotepa, with varying morbidities and success rates. One reported advantage of intrapericardial therapy is that it avoids spread of malignant cells into other body cavities as can occur with surgical or percutaneous approaches. Overall, however, reaccumulation rates in malignancy remain disappointing at 40%.¹⁰

Three surgical approaches to malignant effusion have been described: (1) subxiphoid pericardial “window,” (2) thoracotomy with creation of a pleuropericardial “window,” and (3) thoracotomy with pericardiectomy. Surgery has the additional advantage of allowing tissue to be obtained for diagnostic purposes. However, surgical window procedures, although successful, have reported reaccumulation rates of up to 15% depending on the technique and substantial morbidity (30%) and mortality ($\leq 13.8\%$) rates. Patients with advanced malignancies are often poor candidates for general anesthesia and surgery. In addition, malnutrition- and chemotherapy-related side effects increase the risk of infection and other perioperative complications.¹⁴

Finally, the overall prognosis is poor in this group of patients, with death related to the underlying malignancy estimated at 80% in the reported case series, and increasing their length of hospital stay associated with a surgical procedure may compromise the quality of their remaining lifespan.

In 1991 Palacios et al.¹⁸ first proposed PBP under local anesthesia with conscious sedation as a less invasive alternative technique to surgical pericardial window procedures.

TECHNIQUE OF SINGLE-BALLOON PERCUTANEOUS BALLOON PERICARDIOTOMY

Patients undergoing PBP should undergo informed consent with discussion of pain and discomfort during the procedure, as well as potential complications, including cardiac chamber, coronary artery or cardiac venous injury, pneumothorax, postprocedure pleural effusion, arrhythmia, infection, bleeding, need for emergent cardiac surgery, and death.

The patient's preoperative complete blood count, renal profile (contrast administration and platelet dysfunction), and coagulation profile should be checked in advance of the procedure. The patient's most recent transthoracic echocardiogram should be reviewed in detail; organized or loculated effusions are best managed with surgical pericardial window creation.

Patients typically receive antibiotic prophylaxis with a broad spectrum cephalosporin antibiotic or vancomycin in cases of penicillin allergy or MRSA infection.

Percutaneous balloon pericardiectomy can be significantly painful during balloon inflation and can produce pericarditis-type chest pain after the procedure. Copious local anesthesia to the skin tract as well as generous conscious sedation is recommended.

Percutaneous balloon pericardiectomy can be performed in patients with an existing pericardial drainage catheter and ongoing persistent drainage and de novo for the first time in patients presenting for initial pericardiocentesis. In patients with a preexisting pericardial drainage pigtail catheter, the catheter can be removed over a stiff J-tipped 0.035- or 0.038-inch Amplatz guidewire, leaving the guidewire in the pericardial space. As with pericardiocentesis, the guidewire position should be confirmed by forming a loop within the pericardial space.

The skin tract into the parietal pericardium should be dilated usually up to 10 Fr over the guidewire to allow passage of the dilating balloon catheter. This may cause pain.

Typically, a 12- to 20-mm diameter balloon (Maxi Balloon, Cordis) 3 to 4 cm in length is advanced over the guidewire to the straddle the parietal pericardium. A number of variations on this standard technique have been described, including apical puncture, adjacent side-by-side pericardial balloon placement, double-balloon pericardiectomy, Inoue balloon pericardiectomy, and use of a combination of a long- and short-dilating balloon.¹⁹⁻²⁴

It is important to ensure the proximal end of the balloon is within the subcutaneous tissue and not extending through the skin, which can cause extreme discomfort. The optimal balloon position is confirmed by gentle inflation of the balloon to reveal a waist at the location of the parietal pericardium. The balloon is then manually inflated until the waist disappears. We advocate two to three inflations to ensure successful PBP (Figure 36.3).

Biplane fluoroscopy, if available, should be used to allow fluoroscopic confirmation of the correct positioning of the balloon. If there is difficulty in identifying the parietal pericardium, 5 to 15 mL of radiographic contrast can be injected to identify the pericardial borders. In a left lateral projection, the midpoint of the balloon should be positioned across the parietal pericardial layer.

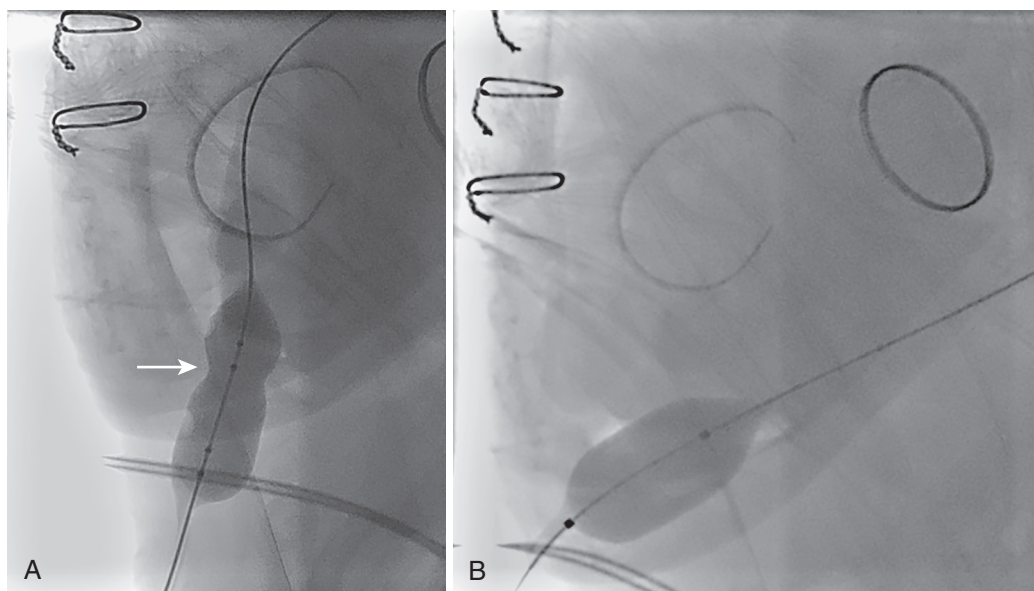


FIGURE 36.3 Percutaneous Balloon Pericardiotomy using a single-balloon technique. Single-balloon technique of percutaneous pericardial window creation using a 20 × 40 mm balloon in this case. On Panel A please note the pericardial outline created by contrast injection into the pericardial space and the residual waist on the balloon (*arrow*) at the site of the parietal pericardial layer. Panel B demonstrates an alternative projection that again demonstrates the pericardial outline created by contrast injection.

If the parietal pericardium is adherent to the chest, with failure of proximal balloon inflation, then a countertraction technique can be used to pull the skin and tissue away from the pericardium as the balloon is advanced forward.

After balloon dilation, the balloon catheter is removed over the stiff 0.035-inch guidewire and replaced with a new pigtail catheter, which is sutured in place.

In the setting of de novo pericardiotomy at the time of pericardiocentesis, the pericardium is entered in standard fashion, and a drainage catheter is placed to allow pericardial pressure measurement. After confirming the opening pericardial pressure, most of the pericardial fluid is aspirated, although some may be left behind to allow ease of position of the balloon dilation catheter.

After PBP, the pericardial catheter should be managed according to the protocol outlined in the pericardiocentesis section. When there is no significant persistent drainage (<75–100 mL/24 hours), the catheter can be removed. Follow-up transthoracic echocardiography should be performed 48 hours after drainage catheter removal. Additionally, chest radiography should be performed to assess for possible pleural effusion development after PBP drainage.

The mechanism by which PBP works remains unclear. It is assumed that localized tearing of the parietal pericardium produces a communication between the pericardial space and the pleural space, the peritoneum, or both. Prior pericardioscopy and radiographic contrast injection analysis has demonstrated a communication between the pericardium and the pleural space.²⁵ Additionally, Chow et al.^{22,26} showed an oval 18.6- × 16.4-mm window after 23-mm Inoue balloon inflation. It is unlikely that a permanent communication persists. It is much more likely that drainage of the pericardial fluid allows the visceral and parietal pericardium to undergo inflammatory fusion.

TECHNIQUE OF DOUBLE-BALLOON PERCUTANEOUS BALLOON PERICARDIOTOMY

The double-balloon technique has emerged as the preferred strategy for balloon pericardiotomy over recent years. In theory, the double-balloon technique creates a larger pericardial window and is better tolerated from a pain perspective than a single large balloon or Inoue balloon. Additionally, balloon rupture is less frequent, removing the risk of the ruptured balloon's becoming lodged in the subcutaneous tissues and the possibility of retained balloon fragments.²⁷

Again, similar to the single-balloon technique, the patient should undergo preprocedural planning with review of the patient's complete blood count, renal profile, and coagulation profile in addition to review of the patient's echocardiogram. Again, loculated effusions should be avoided.

The procedural complications of bleeding, infection, emergent cardiac surgery, pneumothorax, pneumopericardium, persistent left pleural effusion, hemothorax, cardiac vein and coronary artery injury, and cardiac chamber perforation are similar to both pericardiocentesis and the single-balloon technique.

The patient should receive appropriate prophylactic antibiotic coverage as outlined earlier and appropriate periprocedural pain management.

A range of techniques are advocated to access the pericardium. Under ECG, echocardiography, or fluoroscopic guidance, a 4-Fr micropuncture needle, Tuohy needle, or Pajunk needle can be used to access the pericardial space. When the needle tip or tip of the micropuncture sheath is within the pericardial space, agitated saline can be infused and visualized on echocardiography or contrast can be injected to assure correct positioning in the pericardial space.

The skin tract is then serially dilated, and ultimately, a 7-Fr, 13-cm sidearm sheath can be placed into the pericardium.

After this, two 0.035-inch guidewires are introduced into the pericardial space and their position confirmed on fluoroscopy. The authors advocate using either soft-tipped Amplatz Super or Extra stiff guidewires (Cook Medical) or supracore guidewires (Abbott Vascular).

With both guidewires positioned in the pericardial space, the 7-Fr sheath is removed and replaced with two appropriately sized sheaths to accommodate the balloon diameters to be used. Next, an 8- to 12-mm by 20-mm balloon dilatation catheter is advanced over one of the guidewires while a second 8- to 12-mm by 40-mm balloon dilatation catheter is advanced over the second guidewire.

Under fluoroscopy, the position where the two guidewires begin to separate from each other represents the parietal pericardial layer. The balloons are then advanced sequentially to rest across the parietal pericardial layer.

After positioning, the balloons are then inflated sequentially. Each balloon should be inflated slowly to reposition across the parietal pericardium and to ensure they are free of the subcutaneous space. Then the balloons should be maximally inflated. Both balloons should be inflated fully until the balloon waist disappears. Next, with the longer balloon anchored in position, the inflated shorter balloon should be advanced and retracted across the parietal pericardium several times to ensure there is an adequate pericardial window created.

The balloons should then be deflated and removed, and a standard drainage pigtail catheter is placed over either guidewire. Depending on operator preference, contrast media may be injected into the pericardial space to document drainage via the newly created pericardial window into the pleural space. The second guidewire can be removed at this point.

The pericardial drainage catheter should be sutured in position until drainage is minimal. The patient should continue on prophylactic antibiotics. The patient should undergo postprocedure chest radiography to ensure there is no procedural-induced pneumothorax.

OUTCOMES AFTER PERCUTANEOUS BALLOON PERICARDIOTOMY

Palacios et al.¹⁸ first described their initial experience with PBP in eight patients with malignant effusion or tamponade. The procedural success rate was 100%. No immediate or late complications were attributed to the procedure. The mean time to development of a new or significantly increased left pleural effusion was 2.9 ± 0.4 days. The mean follow-up period was $6 \pm$ months. No patients had recurrent effusion or tamponade. However, the prognosis of these patients was poor, in keeping with their underlying primary diagnosis, with death occurring in five cases.¹⁸

A subsequent multicenter registry evaluated the therapeutic role of PBP in 130 patients in 16 centers from 1987 to 1996. Eighty-five percent had a known diagnosis of malignancy (lung carcinoma in the majority), with 58% presenting with cardiac tamponade and had already undergone

pericardiocentesis. PBP was defined as success if there was no recurrence of effusion on echocardiography and if there were no procedural complications. Eighty-five percent (111 of 130) cases were successful, with no effusion recurrences during a mean follow-up of $5 \text{ months} \pm 5.8$ months. Chest tube placement was required in 15% of patients with preexisting effusions compared with 9% in patients without a prior effusion. Of the 104 patients with malignancy, 86 died at a mean time of 3.8 ± 3.3 months after PBP. There were no predictors of survival or freedom from effusion reaccumulation.²⁸

Percutaneous balloon pericardiotomy should be avoided in loculated pericardial effusions because it is unlikely to provide complete drainage. Intrapericardial administration of urokinase or mechanical disruption of fibrinous debris using guidewires and pigtail catheters remains controversial.

Additionally, PBP should be avoided in patients with tenuous pulmonary function because it may result in a significant left pleural effusion, further compromising their lung function.

PERCUTANEOUS PERICARDIAL BIOPSY

As outlined in the earlier sections, large pericardial effusions are a common clinical presentation of a number of disease states. The first step toward definitive diagnosis is pericardiocentesis.

Although helpful, pericardiocentesis provides a definitive diagnosis in only about 25% of cases. Tuberculosis is the most commonly missed diagnosis. In malignant pericardial effusions, fluid cytology results are positive in 50% to 85% of cases, although cell typing remains limited, albeit improving with immunohistochemical staining. To increase diagnostic yield, pericardial biopsy is often required. Traditionally, this has required open surgical biopsy under general anesthesia.¹⁶ Percutaneous techniques for obtaining multiple pericardial tissue samples have been described over the past 20 years.

Percutaneous pericardial biopsy was first performed by Endrys et al.²⁹ in 1988, who reported a series of 18 consecutive patients who needed pericardiocentesis for large pericardial effusion. Using a subxiphoid approach, the authors advanced a 7-Fr Teflon sheath into the pericardial space and drained the pericardial effusion. This sheath was then exchanged for an 8-Fr Teflon sheath with a curved tip and multiple side holes. An endomyocardial biptome was inserted through the sheath, and air was allowed to enter the pericardium to delineate the visceral and parietal pericardium layers. An average of eight separate samples was obtained, with no complications. At the end of the procedure, the air was aspirated, and a drainage catheter was placed as usual. In 9 of the 18 cases, a definitive diagnosis could be obtained from the biopsy specimens.

Mehan et al.³⁰ noted that the floppy nature of the biptome made it difficult to direct toward an appropriate target in the pericardial cavity. Therefore, they modified Endrys et al.'s technique to use the distal portion of 9-Fr Judkins coronary guiding catheter to target specific sites.

Ziskind et al.³¹ subsequently used a similar fluoroscopic approach but used a special pericardial biptome with a central needle and serrated jaws. They did not install air into the pericardial cavity but rather maintained visceral-parietal pericardial separation by not removing all the pericardial fluid at the start of the procedure. In their study of 15 patients, tissue adequate for a tissue diagnosis was obtained in all patients. For patients with a history of malignancy, the addition of biopsy to cytology increased the diagnostic yield from 46% to 62%.³¹ Selig³² further modified the technique using echocardiographic rather than fluoroscopic guidance for biopsy.

Finally, Margey et al.³³ recently described the outcome of pericardial biopsy in seven consecutive patients presenting with suspected malignant effusion. After drainage of the pericardial fluid under fluoroscopic and ECG guidance, they exchanged the pigtail drainage catheter for an 8-Fr, 23-cm braided sheath and subsequently passed a 7-Fr BiPal biopsy forceps (Cordis, Johnson and Johnson) through the sheath and away from the cardiac shadow to the lateral parietal pericardial wall. They obtained a total of five biopsy specimens per procedure without any complications and demonstrated that pericardial biopsy adds incremental diagnostic yield to cytology alone. In this series, biopsy confirmed no malignant invasion in four patients with known malignancy and the presence of lymphocytic and organizing effusive pericarditis in one and two patients, respectively.³³

Percutaneous pericardial biopsy is therefore a less invasive procedure than surgical pericardial biopsy and may be particularly useful in improving the yield of pericardial fluid analysis, especially in patients with malignant and tuberculosis pericardial disease.

TECHNIQUE OF PERCUTANEOUS PERICARDIAL BIOPSY

Pericardial biopsy can either be performed in the setting of a previously drained pericardial effusion with a pigtail

catheter still in place or at the same time as de novo pericardiocentesis.

Standard pericardiocentesis is performed as outlined earlier. Care is taken to ensure that not all of the fluid is drained completely. This is best ascertained on echocardiography or by injection of 5 to 15 cc of radiographic contrast material into the pericardial space.

Adjunctive use of pericardioscopy, outlined later, may help improve the yield of pericardial biopsy by identifying areas of pericardial disease and deposits with direct visualization to target with biopsy.

The pigtail catheter is exchanged over a J-tipped 0.035- or 0.038-inch Amplatz Stiff guidewire for a 7- or 8-Fr, 23-cm braided sheath. The sheath is advanced into the retrocardiac pericardial space and aspirated and flushed. Further local installation of radiographic contrast material can be performed to outline the visceral pericardial layer.

Subsequently, a 7-Fr BiPal Cordis biptome is advanced through the sheath, the jaws opened, and the biptome angled by rotation away from the cardiac shadow toward the parietal pericardial layer. Ideally, this is confirmed in two fluoroscopic planes, usually an anteroposterior and lateral projection (Figure 36.4 and Videos 36.2 and 36.3). Biplane cineangiography capability is useful for this reason. When the operator is satisfied that the biopsy jaws are not directed toward the visceral pericardial layer, up to five biopsy specimens are obtained.

After successful biopsy, the guidewire is readvanced through the sheath into the pericardial space, and the sheath is exchanged for a new drainage pigtail catheter. As outlined earlier, the pigtail is removed when the total drainage is less than 75 to 100 cc per 24 hours.

Although percutaneous pericardial biopsy is less invasive than surgery, it still carries the potential of serious adverse events, particularly when performed without pericardioscopic guidance. If separation of the visceral and parietal pericardial layers cannot be obtained, there is a risk of cardiac laceration or perforation and coronary arterial or venous injury. Additionally, ventricular ectopy, pain, and fever can also occur.

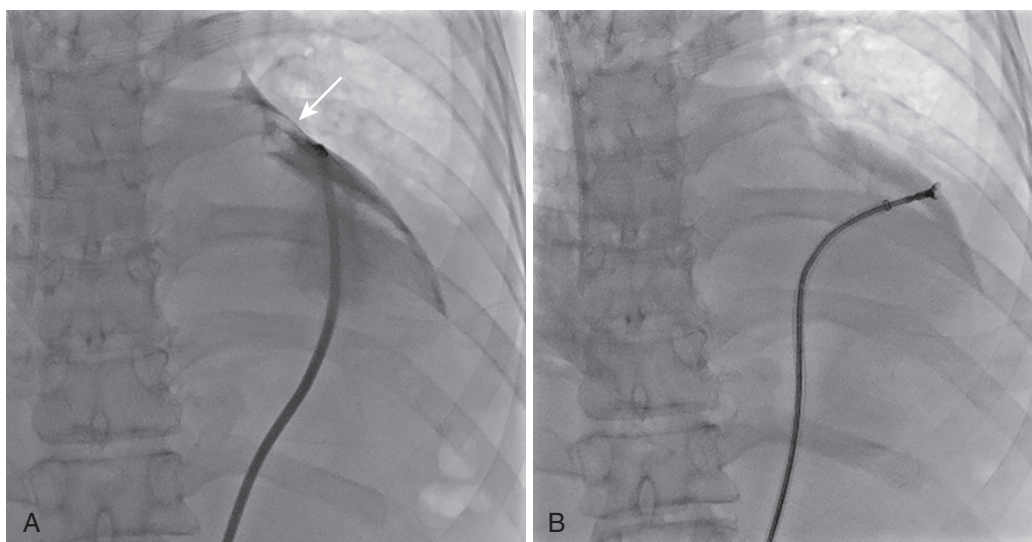


FIGURE 36.4 Percutaneous pericardial biopsy. **A**, Contrast injection through the 8-Fr sheath demonstrating the parietal pericardial layer (arrow). **B**, The BiPal biopsy forceps placed through the sheath and directed toward the parietal pericardium, away from the cardiac surface.

ROLE OF PERICARDIOSCOPY

Seferovic et al.³⁴ reported their experience on the use of pericardioscopy in conjunction with pericardial biopsy to improve the diagnostic yield of isolated fluoroscopy-guided biopsy. Their study included 49 patients with large pericardial effusion undergoing percutaneous biopsy. In 12 cases, standard fluoroscopy was used to guide biopsy, with three to six biopsy samples obtained per case. In 22 patients, four to six biopsies were obtained using pericardioscopy guidance with a 16-Fr flexible endoscope. Finally, in 15 patients, extensive pericardial sampling guided by pericardioscopy was performed, with 18 to 20 samples obtained. Sampling efficiency was significantly better with pericardioscopy versus fluoroscopy (84.9%, 84.2% vs 43.7%). Pericardial biopsy in the extensive sampling group had a much higher yield than fluoroscopy alone in establishing the cause (53.3% vs 8.3%; $P < .05$). The addition of the 16-Fr endoscope access port did not result in any complications.

Therefore, direct visualization of the pericardium for pericardial infiltration or disease deposits may help target biopsy to areas of disease while minimizing the risk of iatrogenic injury.

PERCUTANEOUS EPICARDIAL ACCESS FOR ELECTROPHYSIOLOGY STUDIES AND ABLATION

Epicardial scar-related reentry circuits have been recognized as an important cause of ventricular tachycardia (VT).^{35,36} Approximately 30% of all VT circuits in nonischemic cardiomyopathies, including hypertrophic cardiomyopathy and dilated cardiomyopathy, and 10% to 15% of VTs in ischemic cardiomyopathy, arise from an epicardial circuit. In addition, VT in arrhythmogenic RV cardiomyopathy and Chagas' cardiomyopathy are typically epicardial in origin.³⁷⁻³⁹ Catheter-based intervention techniques in the pericardial space have gained traction since the original series published by Sosa et al.⁴⁰ in 1996 as a modality to perform electrical mapping and ablation of VT.

Additionally, epicardial mapping and ablation also has a role in some atrioventricular reentrant tachycardias, AF (in cases when there is failure to create a transmural lesion by endocardial approaches or if it is not possible to create full isolating encircling lesions around the pulmonary veins because of the pericardial reflections); atrial tachycardia, especially those arising from the LAA; and inappropriate sinus tachycardia.³⁶

A recent multicenter US and separate European registry of epicardial access and ablation reported that epicardial access and ablation is performed in 12% to 17% of all VT ablation procedures in tertiary referral centers.⁴¹

Traditionally, epicardial mapping and ablation has been recommended for cases with prior failed endocardial ablation of VT or in conditions such as Chagas' disease, in which the circuit is typically epicardial. However, recently, epicardial or a combined endoepicardial approach as a first-line therapy has been recommended in cases in which there is an ECG morphology consistent with an epicardial origin, internal electrocardiograms suggestive of an epicardial circuit, or in circumstances of intracardiac thrombus

or a mechanical valve prosthesis that precludes endocardial access.^{35,42,43} Recent multicenter registry data have demonstrated a growing confidence with epicardial ablation as a first-line therapy, with 35% of all epicardial mappings and ablations occurring as first-line treatments and 65% of cases occurring in patients with prior failed endocardial ablation. Long-term freedom from VT can be achieved in 70% to 75% of epicardial ablation procedures.⁴¹

Epicardial access and ablation is usually contraindicated in patients with significant pericardial adhesions from prior cardiac surgery. However, if pericardioscopy or a hybrid surgical subxiphoid pericardial window is performed, then the pericardial adhesions can be divided, and successful epicardial ablation can be performed.^{44,45}

TECHNIQUE OF PERICARDIAL ACCESS AND EPICARDIAL MAPPING AND ABLATION

A standard subxiphoid approach is most commonly used to access the pericardial space. Depending on the location of the electroanatomic substrate (inferior scar versus anterior or lateral scar), either an anterior or inferior (along the diaphragmatic surface) approach with the needle to the pericardial space can be performed.

Typically, either a Tuohy spinal needle with a trochar or a Pajunk needle is used to minimize trauma. Under fluoroscopic or echocardiographic guidance, the needle is advanced toward the pericardium. Typically, the operator works from a shallow left anterior oblique (LAO) projection while checking the right anterior oblique (RAO) view intermittently. It is important to puncture over the mid right ventricle to avoid the base of the heart, where the coronary arteries and veins course, and the apex, which would limit catheter manipulation. Single or biplane projections can be used (Figure 36.5).

When a "give" is felt as the needle enters the pericardial space, the needle trochar can be removed, and the Luer

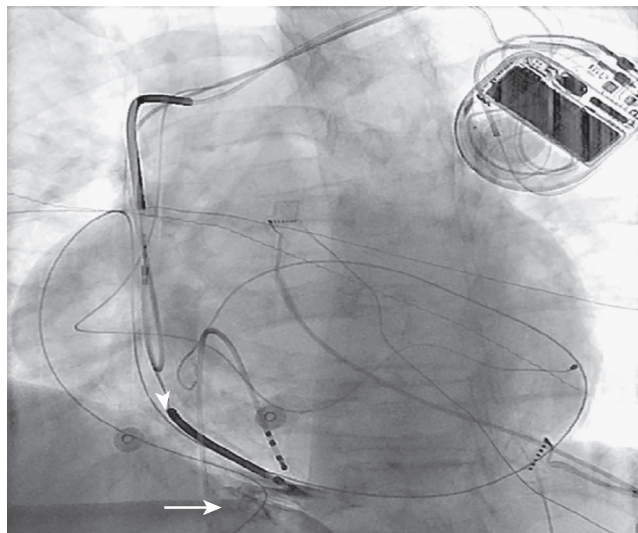


FIGURE 36.5 Pericardial access for epicardial ventricular tachycardia ablation. Note the contrast staining and layering to demarcate the location of the parietal pericardium (arrow). Also note the J-tipped guidewire coiled within the pericardial reflections (arrowhead). (Originally courtesy of Dr. Edmond Cronin, electrophysiologist, Hartford Hospital, Hartford, CT, currently director of electrophysiology, Temple University Hospital, Philadelphia, PA.)

lock syringe with contrast media can be attached. A small injection of contrast is used to demonstrate characteristic layering of fluid within the pericardial space. It is important not to use excessive contrast volumes because doing so will make the needle tip difficult to visualize during further attempts.

The right ventricle is inadvertently entered in up to 17% of cases. If recognized, it rarely results in bleeding, especially if only the needle tip has entered the ventricular wall. However, if not recognized, then in approximately half of cases, there will be substantial pericardial bleeding and possible tamponade.

After successful access to the pericardial space has been confirmed, the syringe can be removed, and a standard 0.032 or 0.035-inch Amplatz guidewire can be advanced into the pericardial space. Demonstration of typical guidewire motion, the absence of premature ventricular ectopics, and tracking of the guidewire across both sides of the septum in the LAO projection helps to confirm access to the pericardial space.

Laham et al.⁴⁶ described a variant of this standard approach in a large animal model of epicardial access. Using a subxiphoid approach and fluoroscopy guidance, continuous positive pressure of 20 to 30 mm Hg, using a saline infusion through the access needle, was used to push the RV wall away from the needle's path and create a potential space to puncture into. In their study of this technique in 49 pigs, no adverse events and no RV injury occurred. However, this technique has not been widely adopted in clinical practice.

After the guidewire position is confirmed, a soft-tipped 7- or 8-Fr sheath is usually placed into the pericardial space. Soft-tipped sheaths are recommended to avoid traumatic coronary artery or vein injury. Furthermore, some authors recommend that the access sheath should not be left empty in the pericardium to prevent trauma. Either the guidewire or a pigtail catheter can be placed through the sheath into the pericardial space. It is recommended to avoid preformed angled or curved access sheaths because these are much more likely to result in cardiac trauma or perforation. If directional support is required, then deflectable-tip catheter sheaths such as the Agilis EPI catheter (St. Jude Medical) can be used.

Electroanatomic mapping can be performed using standard endocardial mapping systems or with a single mapping catheter introduced through the pericardial sheath. Irrigated-tip radiofrequency ablation catheters are preferred because they deliver high power output with less thermal injury. However, because of the continuous irrigation saline infused, the pericardial space should be intermittently drained through the sheath side arm to prevent fluid accumulation and tamponade. Cryoablation catheters have also been used for epicardial ablation.⁴⁷

After completion of the ablation procedure, the sheath is usually left in place, with a pigtail catheter remaining in the pericardial space to minimize cardiac trauma. If there is minimal bleeding and no pericardial aspirate after the procedure, it can be removed. Otherwise, it can be left in place for 24 hours to drain any procedural bleeding.

Most operators instill intrapericardial steroid into the pericardial space and prescribe a course of oral colchicine to minimize sheath- and ablation-induced inflammation and pericarditis.⁴⁸

LIMITATIONS AND POTENTIAL COMPLICATIONS OF PERICARDIAL ACCESS AND EPICARDIAL ABLATION

There are some technical limitations of epicardial ablation. It may not be possible to access all of the posterior pericardial space because of pericardial reflections. Even with current endocardial and epicardial approaches and technologies, some VTs arising from the midmyocardial level may not be possible to ablate. Epicardial fat may attenuate ECG signals and insulate the underlying muscle, making it impossible to effectively deliver ablation energy to the underlying myocardium.

Some degree of subxiphoid and retrosternal pain and discomfort is ubiquitous; however, 30% of patients will experience pericarditis after epicardial procedures. This may be associated with pericardial effusion or even hemorrhagic pericardial effusion. Intrapericardial injection of steroids has been demonstrated to reduce postprocedural pain and pericarditis.⁴⁸

Major complications have been reported in approximately 5% of cases with minor complications reported in 7% to 8% of cases. Complications can be related to the pericardial access or to the mapping and ablation procedures.⁴⁹

Major complications include RV perforation and major pericardial bleeding with tamponade. Dry RV perforation from needle access is reported in up to 17% of cases. RV free wall rupture has also been reported secondary to sheath tip trauma. Other major complications include epicardial bleeding from coronary artery or coronary venous injury requiring emergent surgery, coronary vasospasm and myocardial ischemia, diaphragmatic arterial injury with hemoperitoneum, liver laceration and hepatic hematoma, liver perforation with hemoperitoneum, RV pseudoaneurysm, and rarely, RV-to-peritoneal fistula. Any unexplained intraprocedural hypotension in the absence of pericardial effusion on echocardiography should be investigated further to assess for intrapericardial clot or intraabdominal hemorrhage.

Most operators advocate performing coronary angiography before delivery of ablation therapy to ensure there is no risk of coronary arterial injury with ablation. There is also the risk of phrenic nerve injury, and most operators perform phrenic stimulation testing with high-output pacing via the ablation catheter to ensure no phrenic nerve stimulation before delivering energy.

Minor complications include postprocedural pain, drainable hemopericardium, dry RV puncture with no bleeding, and rarely, left bundle branch block or transient complete heart block. Increasingly, however, epicardial approaches for ablation, in the hands of experienced operators, have grown in volume and become safer overall.

PERCUTANEOUS PERICARDIAL ACCESS FOR transcatheter LEFT ATRIAL APPENDAGE LIGATION

Atrial fibrillation is the commonest arrhythmia worldwide, with a current prevalence of more than 3 million adults in the United States.⁵⁰ An estimated 12 to 16 million Americans

will have a diagnosis of AF by 2050.⁵¹ AF carries a significantly increased risk of morbidity and mortality, with embolic stroke being the most severe manifestation.^{52,53} In patients with AF, there is a fivefold increased risk of stroke. The risk of stroke attributable to AF increases with age, from 1.5% in persons aged 50 to 59 years old to 23.5% in persons aged 80 to 89 years old. The annual incidence of stroke in persons with untreated AF is 4.5%.

The LAA is the prominent source of thrombi in AF, accounting for 90% of thrombi observed in persons undergoing cardioversion.⁵⁴

Currently, oral anticoagulation is the most effective treatment option from stroke prevention (LOE A; Class I).⁵⁵ Unfortunately, only 50% to 60% of patients eligible for warfarin are maintained in the therapeutic window, and there are several drug and dietary interactions with warfarin, making long-term compliance difficult. Novel oral anticoagulant drugs, including dabigatran, apixaban, and rivaroxaban, have demonstrated noninferiority or superiority to warfarin in stroke prevention, without the need for regular blood monitoring. However, these agents still pose a risk of hemorrhagic complications.⁵⁶

Those at highest risk of stroke, in whom anticoagulation is most recommended, can be identified using the CHADS₂-VASc (congestive heart failure, hypertension, age older than 75 years, diabetes, stroke, vascular disease, age 65 to 74 years, and sex category) risk score.^{57,58}

Although anticoagulation is effective at stroke prevention, it does carry a risk of fatal and nonfatal bleeding complications. The risk of bleeding complications increases with age; therefore, the patients who will benefit most from stroke prevention are also the patients most likely to experience bleeding complications.

Therefore, alternative methods of stroke prevention are required in patients with bleeding contraindications to anticoagulation or at high risk of bleeding events, such as patients with recurrent syncope and falls. Exclusion of the LAA has therefore emerged as a potential treatment alternative.⁵⁹⁻⁶¹

Surgical exclusion of the LAA has been advocated for patients intolerant of anticoagulation; as part of a surgical Maze AF ablation; at the time of concomitant coronary artery bypass surgery; or especially, in patients undergoing mitral valve surgery. A number of different surgical techniques and devices are available ranging from simple suture ligation and stapling devices to minimally invasive thoroscopically assisted or robotically assisted epicardial LAA occlusion using the AtriCure AtriClip system (AtriCure). However, the rate of successful occlusion is variable, ranging from 60% to 80% success rates, with residual embolic stroke risk. Additionally, surgical ligation is associated with the risk of postoperative bleeding, perioperative stroke, and LAA laceration.

Several percutaneous approaches to LAA exclusion have therefore emerged. There are at least four endovascular transseptal closure devices developed for LAA exclusion at or completed clinical trial evaluation—the Watchman device (Boston Scientific), Amplatzer Cardiac Plug/Amulet device (St. Jude Medical), Omega device (Eclipse Medical), and PLAATO device (eV3 medical),

which is no longer in production. These devices are effective at occluding the LAA in patients with suitable LAA morphology and are as effective as and safer than continuing long-term anticoagulation with warfarin. However, there are risks of device embolization, device erosion, infection, and thrombus formation on the endovascular side of these devices, which have slowed their widespread adoption.

In 2009, Lee et al.⁶² published a description of a novel endocardial and epicardial approach to suture-mediated LAA exclusion in 26 dogs. The device effectively closed the LAA in 100% of cases. This device, the Lariat percutaneous suture ligation of the LAA (SentreHeart), received US Food and Drug Administration approval for soft tissue closure and is currently marketed for LAA exclusion. It was originally evaluated in a large single-center observational study consisting of 119 patients assessing the efficacy of the LAA closure and procedural safety. Because of anatomic contraindications or intracardiac thrombus, only 85 patients received the LAA exclusion device. Of them, 96% of LAA ligations resulted in complete LAA closure, with the remaining case having less than 2-mm leak on echocardiographic follow-up at 1 year.^{63,64}

PREPROCEDURAL CONSIDERATIONS

Because this procedure requires access to the anterior pericardial space, patients with pectus excavatum, pericardial adhesions and scarring from prior cardiac surgery, radiation, or inflammatory pericardial disease cannot undergo this procedure.

All patients undergo cardiac computed tomography (CT) angiography of the heart and LAA with three-dimensional reconstructions of the appendage. This is helpful to define the shape and size of the appendage. If the width of the appendage is greater than 40 mm, then the device will not be able to pass over the LAA body to ligate its neck or ostium. A larger device for LAA up to 50 mm may be available in the near future. Additionally, CT helps to identify the orientation of the appendage; a superiorly orientated appendage with the LAA apex directed behind the pulmonary trunk is a contraindication to this technique. Last, patients with bilobed or multilobed LAA in which the lobes are oriented in different planes exceeding 40 mm are also not eligible for this device.

Finally, the preprocedural CT scan helps the interventionalist determine the orientation of the LAA and therefore how lateral or anterior the guide sheath needs to be to have the most direct line approach to the distal end of the appendage to position the suture at the LAA ostium. Additionally, CT angiography helps to identify the true deepest apex of the LAA to position the LAA endovascular guidewire as optimally as possible.

Pre- and intraprocedural transesophageal echocardiography (TEE) is not only useful in assessing closure effectiveness but most important also in checking for intracardiac and LAA thrombus before embarking on closure. The presence of intracardiac thrombus is a contraindication to the procedure.

TECHNIQUE OF PERCUTANEOUS TRANSPERICARDIAL LEFT ATRIAL APPENDAGE EXCLUSION

In the majority of institutions, the procedure is performed in the cardiac catheterization laboratory under general anaesthesia with TEE guidance. Single- or biplane fluoroscopy can be used.

The patient should receive broad-spectrum antibiotic prophylaxis with a second- or third-generation cephalosporin or with vancomycin in cases of penicillin allergy or MRSA infection. The patient should discontinue anticoagulation in advance of the procedure.

The Lariat device consists of three components:

1. A 15- to 20-mm compliant occlusion balloon, the EndoCath balloon
2. 0.025- and 0.035-inch magnet-tipped guidewires (FindrWIRZ)
3. A 12- to 14-Fr suture delivery device (LARIAT) with the snare

The procedure involves four basic steps:

1. Pericardial and transseptal access
2. Placement of the endocardial magnet-tipped guidewire in the apex of the LAA with balloon identification of the LAA os
3. Connection of the epicardial and endocardial magnet-tipped guidewires for stabilization of the LAA
4. Snare capture of the LAA with closure confirmation and release of the pretied suture

The technique of pericardial access is similar to that described earlier. Using either a Tuohy spinal needle or a Pajunk needle, from a standard subxiphoid approach, under fluoroscopic guidance, the needle is advanced toward the pericardium. It is essential that the anterior pericardium is accessed. RV angiography can be performed to help identify the RV border as a landmark. Small injections of contrast through the needle can be administered to see typical layering of contrast when the pericardium is entered. Anteroposterior and lateral fluoroscopic projections

can be used to help aid visualization. After the pericardial space has been accessed, a standard 0.035-inch Amplatz guidewire is advanced into the space and confirmed on fluoroscopy. Over this guidewire, the skin tract is dilated, and a 6-Fr sheath can be placed. A second guidewire can then be introduced and left as a precaution in case urgent pericardial drainage is required (Figure 36.6 and Video 36.4). At this point, the 12- to 14-Fr Softip delivery guiding catheter can be advanced over the guidewire into the pericardial space. TEE should be used to confirm location and to assess for effusion and RV compression by the sheath.

After this, transseptal puncture under TEE guidance is performed, and access to the left atrium is established. The ideal location to cross the fossa for this procedure is slightly more posterior and superior than usual. After access to the left atrium is established, the patient should be heparinized with an activated clotting time goal of greater than 250 seconds. An SL-1 sheath can be used to direct anteriorly toward the LAA, and with a pigtail catheter, a left atriogram is performed. This is typically performed in an RAO projection to help identify the ostium and the body of the LAA (Figure 36.7 and Videos 36.5 and 36.6).

After left atrial access has been obtained, the 0.025-inch FindrWIRE with a small curve for steerability is back-loaded into the EndoCath balloon catheter. They are both manipulated to the apex of the LAA under fluoroscopic guidance. The FindrWIRE should be advanced into the distalmost aspect of the LAA, and the proximal balloon marker should be placed just distal to the coronary sinus and circumflex coronary.

The 0.035-inch FindrWIRE magnet-tipped guidewire is then inserted into the pericardial sheath and advanced to the endocardial guidewire in the LAA apex in all form a pathway for the Lariat snare delivery.

After the wires have been connected, the LARIAT is placed over the epicardial guidewire (Figure 36.8 and Video 36.7). The LARIAT is advanced toward the LAA, and the snare is opened and advanced over the LAA. The distal

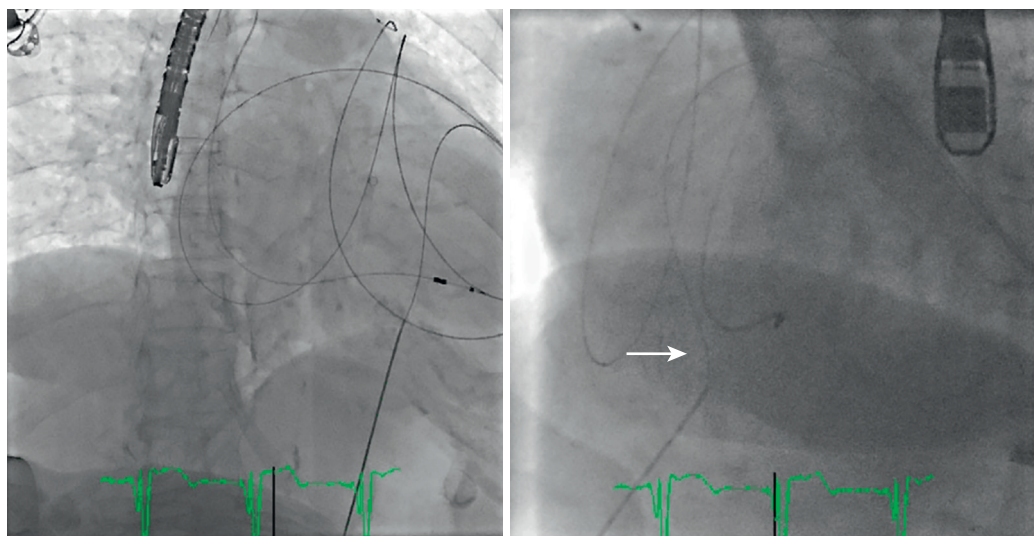


FIGURE 36.6 Percutaneous pericardial left atrial appendage (LAA) occlusion: importance of location of needle access to the pericardium. The two panels depict successful needle access to the pericardium, with coiling of the guidewire within the pericardial space. Note the anterior location and trajectory of the access (arrow), which helps to direct the epicardial delivery sheath and ultimately, the snare delivery system to the LAA.

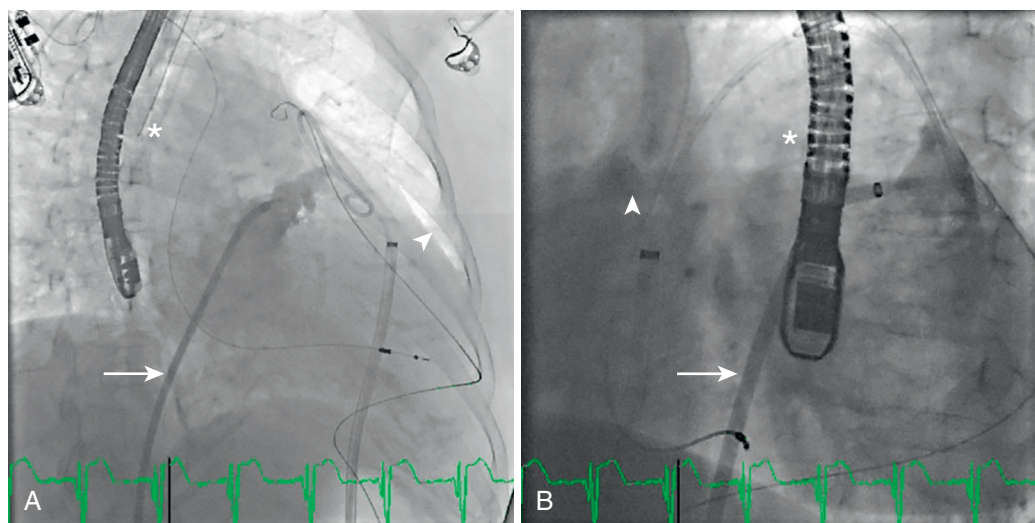


FIGURE 36.7 Percutaneous pericardial left atrial appendage (LAA) occlusion: baseline left atrium/left atrial appendage angiogram. **A**, A right anterior oblique projection. **B**, A left anterior oblique projection. Note the transseptal SL-1 sheath (arrow) placed at the ostium of the LAA. Note also the soft-tipped guiding sheath of the LARIAT delivery system in the pericardial space (arrowheads). Note that there is a pigtail catheter within this to minimize the risk of iatrogenic trauma to a coronary vessel. The procedure is usually performed under transesophageal guidance (asterisk). Last, note there is a second guidewire within the pericardium in case of emergency complications to facilitate prompt pericardial drainage.

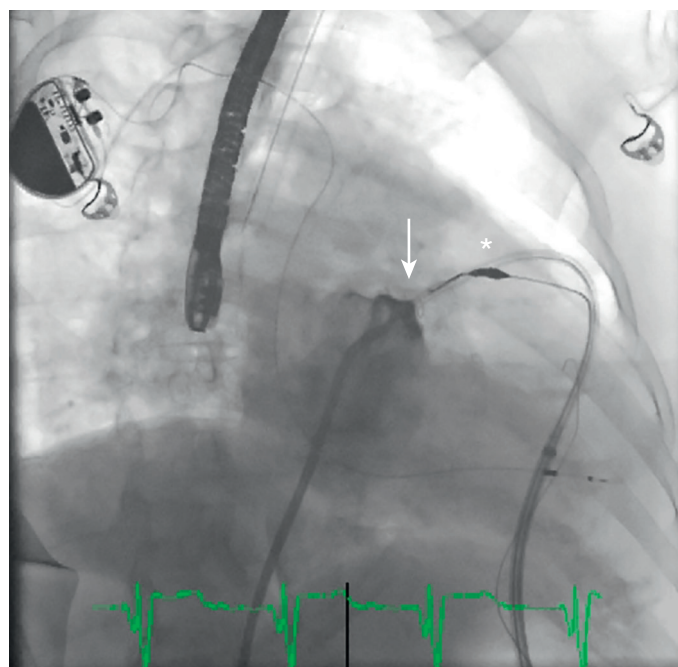


FIGURE 36.8 Percutaneous pericardial left atrial appendage (LAA) occlusion: successful guidewire connection and advancement of the LARIAT snare device over the base of the LAA. After the 0.025- and 0.035-inch magnetized FindrWIRE guidewires are connected at the apex of the LAA (asterisk), the soft-tipped LARIAT delivery system and snare are advanced over the guidewires and slid over the inflated EndoCATH balloon to ensure capture of the true LAA ostium (arrow). Left atrigraphy can be used to help identify the correct positioning of the delivery system.

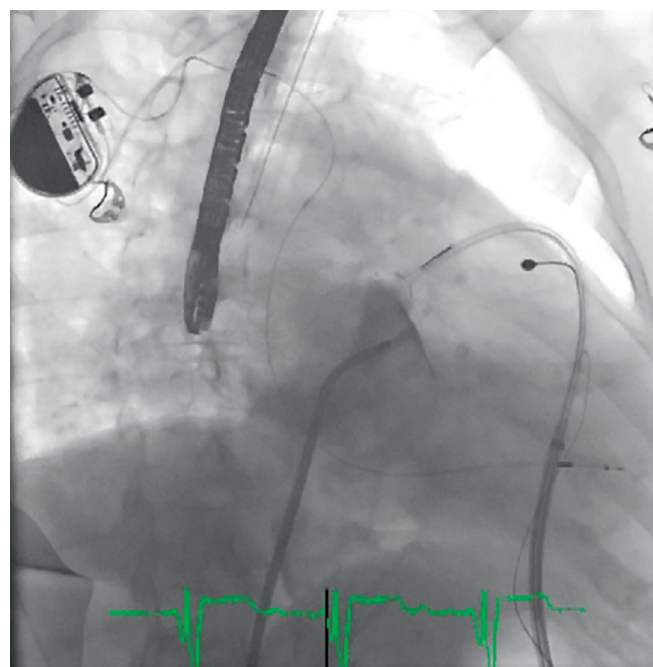


FIGURE 36.9 Percutaneous pericardial left atrial appendage occlusion: successful deployment of the LARIAT snare with completion left atrigraphy. After confirmation of satisfactory positioning on fluoroscopy, atrigraphy, and transesophageal echocardiography, the suture device is tightened, and the snare delivery system is disconnected and withdrawn out of the pericardium.

snare loop of the LARIAT should align with the proximal balloon marker. The balloon is inflated with a 50:50 mixture of contrast and saline. TEE is then used to identify the origin of the LAA. The LARIAT snare is then closed completely. Repeat atrigram and TEE are used to confirm closure and correct snare placement (Figure 36.9 and Video 36.8).

The 0.025-inch FindrWIRE is then withdrawn into the tip of the balloon. The balloon is deflated, and both the Endo-cath and the FindrWIRE are withdrawn as a single unit.

When placement is satisfactory, the LARIAT suture is released and tightened until resistance is met. Two final tightenings are then performed with a suture-tension force gauge, the TenSURE device (SenteHeart).

Both TEE and left atriograms in an RAO and LAO projections can be performed to assess closure. When the LAA is completely excluded, the red suture-release tab is cut and withdrawn over the LAA with snare completely open. Both the LARIAT delivery system and the 0.035-inch FindrWIRE are removed from the guiding cannula, and the remnant suture tail is cut with a remote suture cutter.

Most centers advocate leaving a pericardial drainage catheter in place for at least 6 hours. If there is no drainage at that point, it can be removed safely. If there was inadvertent RV injury or evidence of hemorrhagic effusion, the catheter should remain in place. It is common for patients to develop pericarditis and pericarditis-related pericardial effusion. Intrapericardial steroids in addition to regular nonsteroidal antiinflammatory drugs can be used. Follow-up TEE is recommended at 1 and 6 months because there have been case reports of thrombus formation within small residual LAA leaks.

PROCEDURAL COMPLICATIONS

The commonest procedural side effect is pericarditis, which is reported in up to 30% of patients undergoing the procedure. However, several clinical cases series show that this rarely results in repeat hospitalization, with rates of hospitalization for symptomatic pericarditis after the procedure ranging from 0% to 2.4%. This can result in pericarditis-related pericardial effusion. There are rare reports of effusive-constrictive pericarditis after the procedure.^{63,64} As with any pericardial access technique, there is the potential to injure cardiac chambers, coronary arteries, and cardiac veins, resulting in hemorrhagic effusion, tamponade, and emergent cardiac surgery. With epicardial access, there is the risk of diaphragmatic arterial, hepatic, or inferior vena cava puncture and bleeding. There is also the risk of lacerating the LAA, requiring emergent cardiac surgery. Last, there are isolated reports of persistent LAA leak after LARIAT closure requiring endocardial device occlusion and reports of thrombus formation on the surface of the ligated LAA, usually if there is a small residual pocket.⁶⁵⁻⁷⁰

FUTURE PERSPECTIVES

In the course of the past 3 decades, transpericardial access and interventional techniques, both in structural heart disease and electrophysiology, have rapidly evolved and established themselves in the mainstream. In the future, use of the pericardial route to access the heart will continue to develop with local drug delivery, pacemaker lead delivery for cardiac resynchronization therapy, intrapericardial echocardiography, and further developments in epicardial electrophysiology and structural interventions.⁷¹ The basic technique of accessing the pericardium, which all interventionalists should be familiar and comfortable with, will remain unchanged.

REFERENCES

- Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases; the task force on the diagnosis and management of pericardial diseases of the European Society of Cardiology. *Eur Heart J*. 2015;36:2921-2964.
- Hoit BD. Management of effusive and constrictive pericardial heart disease. *Circulation*. 2002;105(25):2939-2942.
- Jneid H, Maree A, Palacios I. Pericardial tamponade: clinical presentation, diagnosis and catheter-based therapies. In: Parillo J, Dellinger P, eds. *Critical Care Medicine*. 5th ed. Elsevier; 2018.
- Little WC, Freeman GL. Pericardial disease. *Circulation*. 2006;113(12):1622-1632.
- Reddy PS, Curtiss EI, O'Toole JD, Shaver JA. Cardiac tamponade: hemodynamic observations in man. *Circulation*. 1978;58(2):265-272.
- Roy CL, Minor MA, Brookhart MA, Choudhry NK. Does this patient with a pericardial effusion have cardiac tamponade? *JAMA*. 2007;297(16):1810-1818.
- Flannery EP, Gregoratos G, Corder MP. Pericardial effusions in patients with malignant diseases. *Arch Intern Med*. 1975;135(7):976-977.
- Jneid H, Maree A, Palacios I. Acute pericardial disease: pericardiocentesis and percutaneous pericardiomy. In: Mebazza A, Gheorghide M, Zannad F, Parillo J, eds. *Acute Heart Failure*. 1st ed. London: Springer; 2008.
- Sagrìstà-Sauleda J, Angel J, Permanyer-Miralda G, Soler-Soler J. Long-term follow-up of idiopathic chronic pericardial effusion. *N Engl J Med*. 1999;341(27):2054-2059.
- Shepherd FA, Morgan C, Evans WK, Ginsberg JF, Watt D, Murphy K. Medical management of malignant pericardial effusion by tetracycline sclerosis. *Am J Cardiol*. 1987;60(14):1161-1166.
- Sagrìstà-Sauleda J, Angel J, Sambola A, Alguersuari J, Permanyer-Miralda G, Soler-Soler J. Low-pressure cardiac tamponade: clinical and hemodynamic profile. *Circulation*. 2006;114(9):945-952.
- Laham RJ, Cohen DJ, Kuntz RE, Baim DS, Lorell BH, Simons M. Pericardial effusion in patients with cancer: outcome with contemporary management strategies. *Heart*. 1996;75(1):67-71.
- Soler-Soler J, Sagrìstà-Sauleda J, Permanyer-Miralda G. Management of pericardial effusion. *Heart*. 2001;86(2):235-240.
- Fontenelle LJ, Cuello L, Dooley BN. Subxiphoid pericardial window. A simple and safe method for diagnosing and treating acute and chronic pericardial effusions. *J Thorac Cardiovasc Surg*. 1971;62(1):95-97.
- Callahan JA, Seward JB. Pericardiocentesis guided by two-dimensional echocardiography. *Echocardiography*. 1997;14(5):497-504.
- Selig MB. Percutaneous transcatheter pericardial interventions: aspiration, biopsy, and pericardioplasty. *Am Heart J*. 1993;125(1):269-271.
- Marcy PY, Bondiau PY, Brunner P. Percutaneous treatment in patients presenting with malignant cardiac tamponade. *Eur Radiol*. 2005;15(9):2000-2009.
- Palacios IF, Tuzcu EM, Ziskind AA, Younger J, Block PC. Percutaneous balloon pericardial window for patients with malignant pericardial effusion and tamponade. *Cathet Cardiovasc Diagn*. 1991;22(4):244-249.
- Bahl VK, Bhargava B, Chandra S. Percutaneous pericardiomy using Inoue balloon catheter. *Cathet Cardiovasc Diagn*. 1995;36(1):98-99.
- Bertrand O, Legrand V, Kulbertus H. Percutaneous balloon pericardiomy: a case report and analysis of mechanism of action. *Cathet Cardiovasc Diagn*. 1996;38(2):180-182.
- Chow WH, Chow TC, Cheung KL. Nonsurgical creation of a pericardial window using the inoue balloon catheter. *Am Heart J*. 1992;124(4):1100-1102.
- Chow WH, Chow TC, Yip AS, Cheung KL. Inoue balloon pericardiomy for patients with recurrent pericardial effusion. *Angiology*. 1996;47(1):57-60.
- Fakiolas CN, Beldekos DI, Foussas SG, et al. Percutaneous balloon pericardiomy as a therapeutic alternative for cardiac tamponade and recurrent pericardial effusion. *Acta Cardiol*. 1995;50(1):65-70.
- Thanopoulos BD, Georgakopoulos D, Tsaousis GS, Triposkiadis F, Paphitis CA. Percutaneous balloon pericardiomy for the treatment of large, non-malignant pericardial effusions in children: immediate and medium-term results. *Cathet Cardiovasc Diagn*. 1997;40(1):97-100.
- Sugimoto JT, Little AG, Ferguson MK, et al. Pericardial window: mechanisms of efficacy. *Ann Thorac Surg*. 1990;50(3):442-445.
- Chow LT, Chow WH. Mechanism of pericardial window creation by balloon pericardiomy. *Am J Cardiol*. 1993;72(17):1321-1322.
- Iaffaldano RA, Jones P, Lewis BE, Eleftheriades EG, Johnson SA, McKiernan TL. Percutaneous balloon pericardiomy: a double-balloon technique. *Cathet Cardiovasc Diagn*. 1995;36(1):79-81.
- Ziskind AA, Pearce AC, Lemmon CC, et al. Percutaneous balloon pericardiomy for the treatment of cardiac tamponade and large pericardial effusions: description of technique and report of the first 50 cases. *J Am Coll Cardiol*. 1993;21(1):1-5.
- Endrys J, Simo M, Shafie MZ, et al. New nonsurgical technique for multiple pericardial biopsies. *Cathet Cardiovasc Diagn*. 1988;15(2):92-94.
- Mehan VK, Dalvi BV, Lokhandwala YY, Kale PA. Use of guiding catheters to target pericardial and endomyocardial biopsy sites. *Am Heart J*. 1991;122(3 Pt 1):882-883.
- Ziskind AA, Rodriguez S, Lemmon C, Burstein S. Percutaneous pericardial biopsy as an adjunctive technique for the diagnosis of pericardial disease. *Am J Cardiol*. 1994;74(3):288-291.
- Selig MB. Percutaneous pericardial biopsy under echocardiographic guidance. *Am Heart J*. 1991;122(3 Pt 1):879-882.
- Margey R, Suh W, Witzke C, et al. Percutaneous pericardial biopsy- A novel interventional technique to aid diagnosis and management of pericardial

- disease. TCT 477 poster presentation, transcatheter therapeutics 2010. *J Am Coll Cardiol*. 2010;56(suppl):B110.
34. Seferović PM, Ristić AD, Maksimović R, Tatić V, Ostojić M, Kanjuh V. Diagnostic value of pericardial biopsy: improvement with extensive sampling enabled by pericardioscopy. *Circulation*. 2003;107(7):978-983.
 35. Berrueto A, Mont L, Nava S, Chueca E, Bartholomay E, Brugada J. Electrocardiographic recognition of the epicardial origin of ventricular tachycardias. *Circulation*. 2004;109(15):1842-1847.
 36. d'Avila A, Koruth JS, Dukkipati S, Reddy VY. Epicardial access for the treatment of cardiac arrhythmias. *Europace*. 2012;14(suppl 2):ii13-ii18.
 37. Tung R, Michowitz Y, Yu R, et al. Epicardial ablation of ventricular tachycardia: an institutional experience of safety and efficacy. *Heart Rhythm*. 2013;10(4):490-498.
 38. Sarkozy A, Tokuda M, Tedrow UB, et al. Epicardial ablation of ventricular tachycardia in ischemic heart disease. *Circ Arrhythm Electrophysiol*. 2013;6(6):1115-1122.
 39. Pisani CF, Lara S, Scanavacca M. Epicardial ablation for cardiac arrhythmias: techniques, indications and results. *Curr Opin Cardiol*. 2014;29(1):59-67.
 40. Sosa E, Scanavacca M, d'Avila A, Pilleggi F. A new technique to perform epicardial mapping in the electrophysiology laboratory. *J Cardiovasc Electrophysiol*. 1996;7(6):531-536.
 41. Della Bella P, Brugada J, Zeppenfeld K, et al. Epicardial ablation for ventricular tachycardia: a European multicenter study. *Circ Arrhythm Electrophysiol*. 2011;4(5):653-659.
 42. Arenal A, Perez-David E, Avila P, et al. Noninvasive identification of epicardial ventricular tachycardia substrate by magnetic resonance-based signal intensity mapping. *Heart Rhythm*. 2014;11(8):1456-1464.
 43. Fernandez-Armenta J, Berrueto A. How to recognize epicardial origin of ventricular tachycardias? *Curr Cardiol Rev*. 2014;10(3):246-256.
 44. Tschabrunn CM, Haqqani HM, Cooper JM, et al. Percutaneous epicardial ventricular tachycardia ablation after noncoronary cardiac surgery or pericarditis. *Heart Rhythm*. 2013;10(2):165-169.
 45. Soejima K, Couper G, Cooper JM, Sapp JL, Epstein LM, Stevenson WG. Subxiphoid surgical approach for epicardial catheter-based mapping and ablation in patients with prior cardiac surgery or difficult pericardial access. *Circulation*. 2004;110(10):1197-1201.
 46. Laham RJ, Simons M, Hung D. Subxiphoid access of the normal pericardium: a novel drug delivery technique. *Catheter Cardiovasc Interv*. 1999;47(1):109-111.
 47. Nagashima K, Watanabe I, Okumura Y, et al. Epicardial ablation with irrigated electrodes: effect of bipolar vs. unipolar ablation on lesion formation. *Circ J*. 2012;76(2):322-327.
 48. Dyrda K, Piers SR, van Huls van Taxis CF, Schalij MJ, Zeppenfeld K. Influence of steroid therapy on the incidence of pericarditis and atrial fibrillation following percutaneous epicardial mapping and ablation for ventricular tachycardia. *Circ Arrhythm Electrophysiol*. 2014;7:671-676.
 49. Koruth JS, Aryana A, Dukkipati SR, et al. Unusual complications of percutaneous epicardial access and epicardial mapping and ablation of cardiac arrhythmias. *Circ Arrhythm Electrophysiol*. 2011;4(6):882-888.
 50. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22(8):983-988.
 51. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114(2):119-125.
 52. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98(10):946-952.
 53. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154(13):1449-1457.
 54. Thambidorai SK, Murray RD, Parakh K, et al. Utility of transesophageal echocardiography in identification of thrombogenic milieu in patients with atrial fibrillation (an ACUTE ancillary study). *Am J Cardiol*. 2005;96(7):935-941.
 55. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;123(10):e269-e367.
 56. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation*. 2011;123(21):2363-2372.
 57. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation. *JAMA*. 2001;285(22):2864-2870.
 58. Puwanant S, Varr BC, Shrestha K, et al. Role of the CHADS2 score in the evaluation of thromboembolic risk in patients with atrial fibrillation undergoing transesophageal echocardiography before pulmonary vein isolation. *J Am Coll Cardiol*. 2009;54(22):2032-2039.
 59. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. *Heart*. 1999;82(5):547-554.
 60. Veinot JP, Harrity PJ, Gentile F, et al. Anatomy of the normal left atrial appendage: a quantitative study of age-related changes in 500 autopsy hearts: implications for echocardiographic examination. *Circulation*. 1997;96(9):3112-3115.
 61. Faletra FF, Nucifora G, Regoli F, Ho SY, Moccetti T, Auricchio A. Anatomy of pulmonary veins by real-time 3D TEE: implications for catheter-based pulmonary vein ablation. *JACC Cardiovasc Imaging*. 2012;5(4):456-462.
 62. Lee RJ, Bartus K, Yakubov SJ. Catheter-based left atrial appendage (LAA) ligation for the prevention of embolic events arising from the LAA: initial experience in a canine model. *Circ Cardiovasc Interv*. 2010;3(3):224-229.
 63. Bartus K, Bednarek J, Myc J, et al. Feasibility of closed-chest ligation of the left atrial appendage in humans. *Heart Rhythm*. 2011;8(2):188-193.
 64. Bartus K, Han FT, Bednarek J, et al. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. *J Am Coll Cardiol*. 2013;62(2):108-118.
 65. Baker MS, Paul Mounsey J, Gehi AK, Chung EH. Left atrial thrombus after appendage ligation with LARIAT. *Heart Rhythm*. 2014;11(8):1489.
 66. Briceno DF, Fernando RR, Laing ST. Left atrial appendage thrombus post LARIAT closure device. *Heart Rhythm*. 2014;11(9):1600-1601.
 67. Keating VP, Kolibash CP, Khandheria BK, Bajwa T, Sra J, Kress DC. Left atrial laceration with epicardial ligation device. *Ann Thorac Cardiovasc Surg*. 2014;(suppl 20):904-908.
 68. Koneru JN, Badhwar N, Ellenbogen KA, Lee RJ. LAA ligation using the LARIAT suture delivery device: tips and tricks for a successful procedure. *Heart Rhythm*. 2014;11(5):911-921.
 69. Koranne KP, Fernando RR, Laing ST. Left atrial thrombus after complete left atrial appendage exclusion with LARIAT device. *Catheter Cardiovasc Interv*. 2015;85(2):E54-E57.
 70. Mosley WJ II, Smith MR, Price MJ. Percutaneous management of late leak after lariat transcatheter ligation of the left atrial appendage in patients with atrial fibrillation at high risk for stroke. *Catheter Cardiovasc Interv*. 2014;83(4):664-669.
 71. d'Avila A, Neuzil P, Thiagalingam A, et al. Experimental efficacy of pericardial instillation of anti-inflammatory agents during percutaneous epicardial catheter ablation to prevent postprocedure pericarditis. *J Cardiovasc Electrophysiol*. 2007;18(11):1178-1183.



37

Adult Congenital Heart Disease: Cardiovascular Interventions For Pulmonary Arterial Hypertension, Anomalous Vascular Connections, Aortic Coarctation, And Pulmonary Valve Replacement

JOHN F. RHODES, JR.

ADULT CONGENITAL HEART DISEASE, 679

ADULTS WITH CONGENITAL HEART DISEASE: CATHETER INTERVENTIONS, 679

Pulmonary Arterial Hypertension, 679

Anomalous Vascular Connections, 681
Coarctation of the Aorta, 683

Pulmonary Valve Replacement, 685

CONCLUSIONS, 688

ADULT CONGENITAL HEART DISEASE

The adult congenital heart disease (ACHD) patient population is expanding.¹ These patients are living with either native or repaired ACHD and often require cardiovascular catheterization.¹ Therefore, common catheter interventions for patients with ACHD are described in this chapter.

Catheter interventions for patients with ACHD are performed with either a general anesthetic or moderate sedation using a standard Seldinger technique and anticoagulation with a goal activated clotting time (ACT) of 200 to 250 seconds or greater. Antibiotics for bacterial endocarditis prevention are indicated for patients receiving implanted devices based on guidelines.¹

Baseline hemodynamics are obtained in ambient air, thus precluding a pulmonary venous saturation. Consequently, this saturation can be assumed 95% in the presence of a right-to-left shunt or the same as the arterial saturation if no shunt. Subsequently, the ratio of pulmonary blood flow (Qp) to systemic blood flow (Qs) is calculated according to the following formula: $Qp/Qs = [(Ao_2 - MVo_2)/(PVo_2 - Pao_2)]$ in which Ao_2 is the aortic oxygen saturation, MVo_2 is the mixed venous oxygen saturation, Pao_2 is the pulmonary arterial saturation, and PVo_2 is the pulmonary venous saturation. After hemodynamics, angiography is performed to further delineate the anatomy or lesion severity.

ADULTS WITH CONGENITAL HEART DISEASE: CATHETER INTERVENTIONS

Pulmonary Arterial Hypertension

Overview

Pulmonary vasculature alterations are common in patients with ACHD and can be related to the presence or history of increased pulmonary flow secondary to left-to-right shunts as well as distortion of the pulmonary arteries caused by previous interventions or surgical procedures.² Pulmonary arterial hypertension (PAH), defined as mean pulmonary artery (PA) pressure of 25 mm Hg or greater, occurs in 4% to 10% of patients with ACHD and increases in occurrence with advanced age.³ Pulmonary angiography is performed if there are concerns for diminished pulmonary segmental anatomy or PA stenoses. Right heart hemodynamics are obtained to conclude the type of PAH as having a precapillary, postcapillary, or mixed pre- and postcapillary cause (Table 37.1). These hemodynamic data are also used for assessment of clinical severity of right heart derangements and for selection regarding heart or heart and lung transplantation.³ Important hemodynamics that predicts outcome include the cardiac filling pressure ratio calculated as mean right atrial (RA) pressure/mean pulmonary capillary wedge pressure (PCWP) with normal less than 1.0 and the pulmonary artery pulsatility index (PAPi) calculated as PA pulse pressure/mean RA pressure with normal greater than 2.0 (Table 37.2).

TABLE 37.1 Pulmonary Hypertension Types

PULMONARY HYPERTENSION (MEAN ≥ 25 mm Hg)	MEAN PCW (mm Hg)	TPG (MEAN PA TO PCW) (mm Hg)	DPG (PA DIASTOLIC TO PCW) (mm Hg)	PVRI (WOOD units/m ²)
Precapillary	<15	>10	>7	>4
Postcapillary	≥ 15	≤ 10	≤ 7	≤ 4
Mixed pre- and postcapillary	≥ 15	$>10^a$	$>7^a$	$>4^a$

^aCan be all or part of these three data.

DPG, Pulmonary artery diastolic pressure gradient; PA, pulmonary artery; PCW, pulmonary capillary wedge; PVRI, Pulmonary vascular resistance indexed; TPG, transpulmonary gradient.

TABLE 37.2 Cardiovascular Hemodynamics

HEMODYNAMIC DATA	ASSESSMENT	NORMAL	SEVERE ^a
Cardiac index	Cardiac output/BSA	3–5 L/min/m ²	<2 L/min/m ²
Cardiac filling pressure	Mean RAP	<12 mm Hg	>20 mm Hg
Cardiac filling pressure ratio	Mean RAP/PCW	>1.0	<1.0
PVRI	(Mean PA – mean PCW)/Qp	<4 WU/m ² <2.3 WU	>8 WU/m ² >4.6 WU
Pulmonary artery pulsatility index	(PA systolic – diastolic)/RAP	>2.0	<1.0
Shunt magnitude	Qp/Qs ratio	1:1	>1.5

^aData for severe right heart abnormalities.

BSA, Body surface area; PA, pulmonary artery; PCW, pulmonary capillary wedge; PVRI, pulmonary vascular resistance indexed; Qp/Qs, pulmonary-to-system flow ratio; RAP, right atrial pressure; WU, Wood unit.

Pulmonary vascular reactivity testing is performed after 10 minutes of 100% oxygen and 40 ppm of nitric oxide. A positive vasoactivity response to pulmonary vasodilator testing is considered when there is a 30% or greater decrease in baseline PVRI or a mean PA pressure reduction of 10 mm Hg or greater to reach an absolute value less than 40 mm Hg.

If patients have an associated shunt lesion with a resting right-to-left shunt or pulmonary vascular resistance greater than 8 Wood units, closure of the shunt should be carefully evaluated and is a Class III recommendation.³ Transient balloon occlusion is performed to assess the cardiac output, pressures, and resistance (Table 37.3).

Patients with d-transposition of the great arteries after atrial switch (Mustard or Senning operation) and mixed or postcapillary pulmonary hypertension and pulmonary venous baffle obstruction should be assessed by simultaneous PCWP and systemic ventricular end-diastolic pressure gradient as well as angiography. When pulmonary venous baffle obstruction is confirmed, transbaffle puncture using transesophageal echocardiography (TEE) or intracardiac echocardiography guidance can be performed followed by intracardiac pulmonary venous baffle stent angioplasty to relieve the postcapillary pulmonary hypertension.

TABLE 37.3 Clinical Guidelines for Hemodynamic Evaluation

PVRI
Normal <4 Wood units/m ²
Pulmonary Hypertension
Mean PA pressure >25 mm Hg
Precapillary/right heart = mean PCWP <12–15 mm Hg
Postcapillary/left heart = mean PCWP >12–15 mm Hg
Moderate PVRI Risk Level
PVRI = 4–8 Wood Units/m ²
Severe PVRI Risk Level
PVRI >8 Wood units/m ²
Positive Vasoactivity Response to Pulmonary Vasodilator Testing
>30% decrease in baseline PVRI
Mean PA pressure reduction of ≥ 10 mm Hg to reach an absolute value of ≤ 40 mm Hg
Shunt Magnitude
Intervene generally when Qp/Qs $\geq 1.5:1$
Intervention contraindicated if net right-to-left shunt

PA, Pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; Qp/Qs, pulmonary-to-system flow ratio.

Eisenmenger Syndrome

More than half of patients with ACHD with PAH have insults over time that produce progressive structural changes in the pulmonary vasculature.⁴ These changes consist of medial thickening and hypertrophy, endothelial damage, and in situ thrombosis, resulting in an increase in pulmonary vascular resistance caused by the decrease in the cross-sectional area of the pulmonary circulation and vasoconstriction. In patients with unrepaired ACHD, the pulmonary vascular changes continue to worsen.⁴ Consequently, the decreasing left-to-right shunt and increasing right-to-left shunt result in progressively worse systemic hypoxemia, erythrocytosis, cyanosis, and clubbing. Eisenmenger syndrome refers to this reversal of the shunt caused by the development of pulmonary vascular disease.⁴ Patients present with syncope, palpitation, hyperviscosity symptoms, hemoptysis, stroke, or brain abscess.³

Patients are advised to avoid dehydration, heavy exertion, and systemic vasodilators that can increase the right-to-left shunting. If a surgical procedure is planned, careful cardiac anesthetic management should be available, and use of air filters for intravenous access to avoid paradoxical air embolism is mandatory. Avoidance of hypotension is important; otherwise, the degree of right-to-left shunting will increase, and progressive hypoxemia will develop, with a risk of death. If coronary angiography is needed, the most experienced operator should perform the procedure with minimal contrast to minimize the risk of kidney failure. Cyanotic patients are more susceptible to developing nephropathy with the use of contrast, nonsteroidal antiinflammatory drugs, or other drugs such as aminoglycosides.³

Atrial Septoplasty

Atrial septoplasty using a graded balloon dilation technique is recommended for patients with severe PAH but

should be avoided in those with end-stage PAH with severe right heart failure.³ This technique requires (1) transseptal atrial wall puncture using a standard technique, (2) atrial septal angioplasty using an 8-mm peripheral cutting balloon (Boston Scientific), and (3) high-pressure balloon angioplasty using a 14- to 18-mm balloon to extend the atrial defect diameter. This technique creates a 4- to 6-mm interatrial right-to-left “pop-off,” decreasing RA pressure, augmenting left ventricular preload, and improving cardiac output, thus decreasing sympathetic hyperactivity. A newer technique includes use of an atrial flow regulator device currently available through an ongoing clinical trial (NCT03022851).

Atrial Flow Regulators

More recently, Rajeshkumar et al.⁵ published initial results for 12 patients with a mean age of 28 years. The patients were implanted with an atrial flow regulator for severe PAH, syncope, and right heart failure. All of the procedures were successful with no serious adverse events. During follow-up, the atrial flow regulator device remained patent in each patient, and oxygen saturations decreased significantly during exercise from a mean of 98% to 85%, and 6-minute walk tests improved significantly.

Anomalous Vascular Connections

Coronary Artery Fistulae

Coronary artery fistulae (CAF) are connections between the coronary arteries and a cardiac chamber or great vessel resulting in a “steal” away from the myocardium. They are usually discovered during routine cardiac catheterization or cardiac computed tomography (CT) during coronary angiography and are predominately asymptomatic requiring no therapy.⁶ The majority originate from the right coronary artery, with the left anterior descending and circumflex coronary arteries less common, and terminate into the right side of the heart.

The diagnosis can be suspected when a continuous murmur is detected, and on rare occasions, the steal from the myocardium results in angina symptoms. Diminished distal coronary perfusion can be demonstrated during exercise testing with imaging methods. It is uncommon for CAF to be large enough that a substantial left-to-right shunt is present, and often no oximetric step-up can be demonstrated.⁶ Reported symptoms caused by a CAF include steal from the adjacent myocardium, causing myocardial ischemia, cardiac failure, atrial fibrillation, or endarteritis.⁶ Other reported rare complications include thrombus within the fistula, leading to acute myocardial infarction or ventricular arrhythmias, and spontaneous rupture of the aneurysmal fistula causing hemopericardium.⁶

The catheter-based intervention approach can be femoral or radial artery. A venous sheath should be considered for when a rail wire technique or retrograde approach to deliver the occlusion device is deemed necessary. Selective coronary angiography is performed to confirm the diagnosis and delineate the anatomy of the CAF (Figure 37.1 and Video 37.1). Detailed angiographic views in multiple projections are essential to the safe and effective treatment of a CAF.

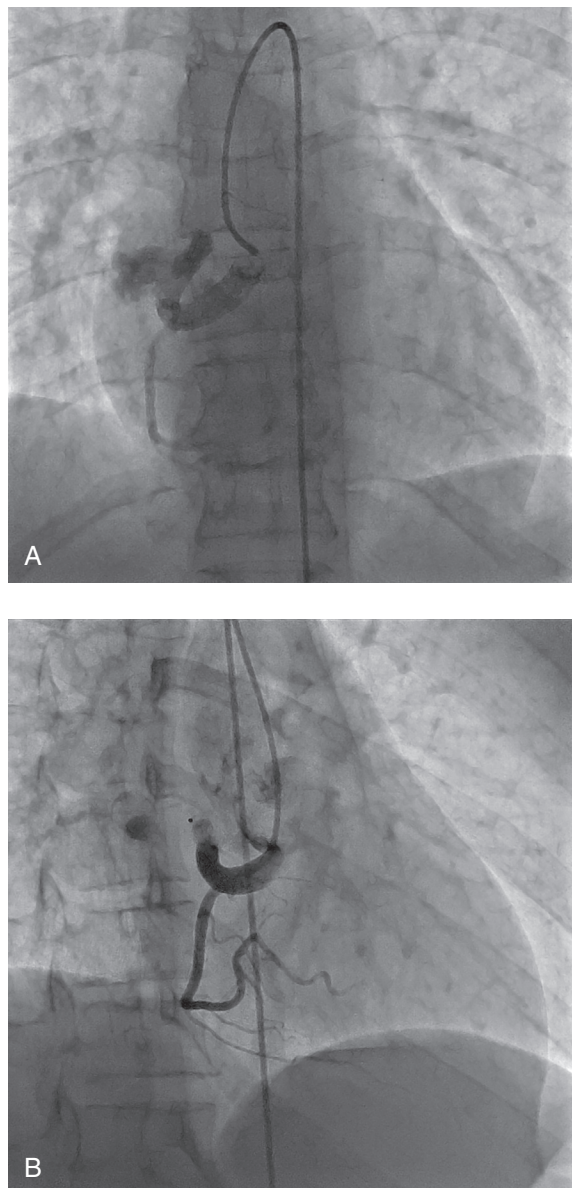


FIGURE 37.1 **A**, Right coronary artery angiogram with proximal coronary dilation due to a fistula to the superior vena cava and right atrium. **B**, Right coronary artery angiography post occlusion device placement at the entrance of the fistula to the superior vena cava and right atrium.

Transcatheter intervention is indicated when there is evidence for coronary steal and clinical symptoms (Table 37.4). CAF occlusion can be accomplished using various implantation techniques, including various types of coils or vascular plugs depending on vessel size and shape.⁶ The goal of treatment of CAF is complete fistulae occlusion with an improved and unobstructed coronary flow pattern. Catheter closure should be distal within the fistula to avoid obstruction of coronary branches or clot propagation.

The recommended technique is a coaxial system using a coronary guide catheter of proper size and shape (usually 6–8 Fr) advanced to the ostium of the involved coronary artery with a second catheter within this guide catheter (4- or 5-Fr hemodynamic catheter) to advance a wire distally within the CAF. A rail technique using a snare catheter from the venous access can secure the wire position. Then an end-hole wedge balloon catheter is passed over this

TABLE 37.4 Adult Congenital Interventions for Vascular Occlusion

	INDICATION	METHODS	ACUTE SUCCESS	COMMENTS
Coronary fistulae	Evidence for coronary steal	Coil occlusion	Technically high	Complications include unwanted branch occlusion or embolization
Pulmonary AV fistulae	Cyanosis Evidence of paradoxical emboli	Coil occlusion Occasionally, Amplatzer or other occluder if fistula large	Technically high in selected lesions	Often multiple small fistulae present that are not amenable to coil occlusion Regrowth of collaterals high
Venovenous collaterals	Evidence of systemic hypoxemia or systemic embolic events	Coil occlusion if small or Amplatzer plug or PDA device if large collateral	Technically high in selected lesions	High long-term success rate Complications include residual leak, hemolysis, and embolization

AV, Arteriovenous; PDA, patent ductus arteriosus.

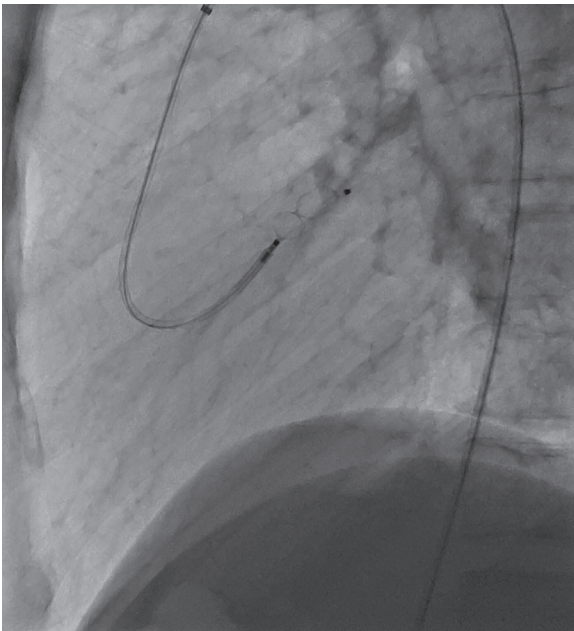


FIGURE 37.2 Coronary artery fistula closure with a single Vascular Plug IV device.

wire (retrograde or antegrade), leaving the guide catheter at the ostium of the coronary artery. The balloon is positioned distal to the last viable myocardial branch and is inflated with contrast to temporarily occlude the vessel for 5 to 10 minutes to assess the risk of ischemia with fistula occlusion. With large CAF, this may not be possible to accomplish. If no detectable ischemic changes are noted, then the choice of occlusion technique is based on the size and shape of the CAF. Coils or devices can be used to close the CAF. If coils are chosen, they can be deployed antegrade from the aortic guide catheter with the delivery catheter telescoped within the guide catheter and positioned distal within the CAF. If devices are chosen, the wire can be snared and exteriorized from either femoral or jugular vein, and the proper size sheath is advanced into the fistula and then the device is advanced from the vein to the distal fistula. The aortic guide catheter is used for selective coronary injections to guide the deployment site and to assess feeding vessels.

Complete occlusion of the fistula can be achieved in more than 95% of patients (Figure 37.2 and Video 37.2). In

the remaining patients, either further procedures may be required or managed conservatively if the residual fistulas are small. Serious adverse events are uncommon but include embolization (within the coronary arteries), neurologic events (systemic embolus), transient bundle branch block, and myocardial infarction.⁶ Coil or thrombus migration remains the most common serious adverse event, and thus recent recommendations are to consider the use of detachable coils and use antiplatelet agents or anticoagulation after occlusion to prevent thrombosis and closure of the larger main coronary arteries. Currently, catheter closure of CAF is considered a safe and effective alternative to surgery.⁶

Pulmonary Arteriovenous Malformations

Pulmonary arteriovenous malformations (PAVM) are abnormal communications between pulmonary arteries and pulmonary veins.⁷ PAVM can either be congenital or acquired, but the cause is often difficult to differentiate. PAVM is especially common in patients with inadequate pulmonary blood flow containing systemic hepatic venous return. This occurs with various congenital heart defects but is common after a bidirectional Glenn (superior vena cava anastomosed to the right PA) for single-ventricular physiology.⁷ PAVMs are also particularly common in patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)⁷ and are found in nearly 5% of patients with migraine headache with aura.⁷ Multiple small fistulae may also be seen in patients with hepatopulmonary syndrome.⁷ The clinical presentation varies between no symptoms to severe illness. The most common clinical presentation includes epistaxis, dyspnea, and hemoptysis. Systemic hypoxemia may occur from the right-to-left shunt (Figure 37.3A and Video 37.3A), and the resultant shunt may lead to paradoxical embolus resulting in stroke or transient ischemic attack.

When PAVMs are large enough (>2 mm) or create either systemic hypoxemia or evidence for systemic embolization, then transcatheter occlusion⁸ may be used (Figure 37.3B and Video 37.3B). Transcatheter occlusion of PAVF is considered the mainstay of treatment,⁸ and the technique is like closure of the CAF. The most used technique uses a Vascular Plug I, II, or IV (Abbot Medical). Embolization of all entry vessels to the malformation is critical to prevent recanalization. The risk of migration through the malformation into

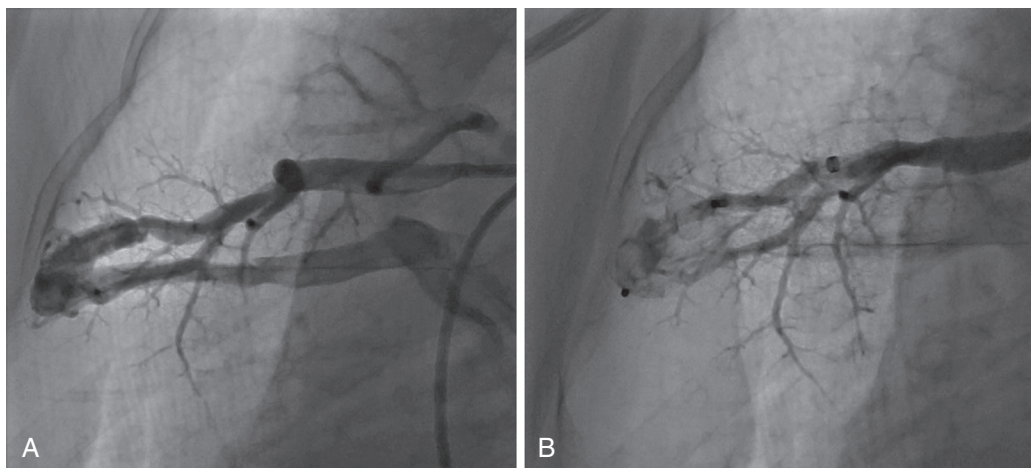


FIGURE 37.3 **A**, Cineangiogram showing a large pulmonary arteriovenous malformation (PAVMs) within the right lung segments with significant systemic hypoxemia caused by right-to-left shunting. **B**, Cineangiogram after closure of PAVMs in the right lung segments with a Vascular Plug IV.

systemic circulation has been decreased significantly with these more recent occlusion devices.

Anomalous Venous Connections: Systemic Hypoxemia

Anomalous venovenous connections may occur in patients with elevated systemic venous pressures, such as those who have had the Glenn or Fontan operation or patients with stenoses or occlusions of the main systemic veins. Often these collaterals connect the left for right innominate vein or other systemic venous structures to the pulmonary veins or directly to the left atrium. Like patients who have persistent fenestrations, patients with venovenous collaterals manifest clinically as having systemic hypoxemia, with or without exercise, or a route for systemic embolic events. The standard angiograms to assess the systemic venous circuit for these malformations is a 10- to 25-cc biplane cineangiogram in the inferior vena cava distal to the hepatic veins, a biplane cineangiogram at the proximal anastomosis of the Fontan or Glenn pathway, a biplane cineangiogram in the left innominate vein for patients with right-sided Glenn shunts, and angiograms in both superior vena cava in patients with bilateral Glenn shunts. If these angiograms do not demonstrate the explanation for the patient's systemic hypoxemia or embolic events, we recommend agitated saline injections in the proximal right and left pulmonary arteries with simultaneous TEE or chest wall echocardiography to assess for tiny arteriovenous malformations in either lung. The lung with the least or no blood from including the hepatic veins is most likely to have these later malformations. Transcatheter closure of the venovenous fistulae or larger arteriovenous malformations can be performed using Gianturco coils, vascular plugs, or vascular occlusion devices. Final angiography or agitated saline injections can be used to assess for immediate closure, and systemic oxygen saturations at rest or during follow-up exercise testing can be checked to confirm improvement and future risk for embolic events. Transcatheter coil occlusion of these anomalous channels has been used successfully to reduce the right-to-left shunt.

Coarctation of the Aorta

Overview

Coarctation of the aorta (CoA) is either native or recurrent, with history of a previous surgical repair. Bicuspid aortic valve is associated with CoA in 50% to 85% of patients,⁹ and a significant aortic valve gradient is particularly important to exclude when deciding on definitive therapy. The natural history suggests that CoA represents a more diffuse arteriopathy involving arterial wall stiffness and renal hypoperfusion leading to a resetting of the renin-angiotensin system and a hyper-renin state that may not abate even after relief of the coarctation.⁹ Also, cerebrovascular events related to cerebral aneurysm rupture have been reported before and after relief of aortic coarctation.⁹ Unfortunately, with unrepaired coarctation, the mean survival time is reported at approximately 35 years⁹ with life expectancy beyond the sixth decade being unusual.

The coarctation site is typically at the aortic isthmus beyond the origin of the left subclavian artery across from the ampulla of the ligamentous arteriosus. Collateral circulation often is present to bypass the obstructed aortic segment and provide blood flow to the lower body. The most common origins for these collaterals are from the subclavian arteries through the internal thoracic arteries and the thyrocervical and costocervical branches. These vessels communicate with the intercostal arteries, which then perfuse the descending aorta distal to the obstructed aortic segment. This can produce diminished but palpable lower extremity pulses and mask a severely obstructed aorta.

Before the catheterization and during follow-up, transthoracic echocardiography can be used to interrogate the descending aorta, with a resting peak systolic velocity of 3.2 m/s or greater or a diastolic velocity of 1.0 m/s or greater suggestive of significant aortic obstruction. Echocardiography also allows interrogation of the aortic valve and assessment of the ascending aortic root. Additional imaging with magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) has become the imaging modality of choice both before and after catheterization to assess the aorta and evaluate the coarctation segment. MRI provides



FIGURE 37.4 Computed tomography image of discrete coarctation of the aorta at the isthmus.

anatomic data regarding the aortic valve and ascending aorta. CT with contrast also provides an acceptable alternative. Multidimensional CT allows for three-dimensional reconstruction like MRA (Figure 37.4 and Video 37.4).

Asymptomatic patients with exercise peak systolic blood pressure greater than 220 mm Hg, an upper-to-lower extremity BP gradient greater than 20 mm Hg, or peak-to-peak gradient greater than 20 mm Hg meet guidelines for intervention.¹ Also, symptomatic patients or patients with low cardiac output with a lesser gradient and left ventricular hypertrophy should be considered for intervention.¹ Other evolving indications for intervention include the presence of aortic aneurysms, symptomatic aneurysms of the circle of Willis, and women considering pregnancy to prevent inadequate placental blood flow.

Recurrent CoA after surgical repair can be caused by aortic narrowing within the surgical site (Figure 37.5 and Video 37.5) or hypoplasia of the transverse arch proximal to the CoA repair. These latter obstructive lesions are subcategorized as either proximal transverse arch (between the innominate artery and left carotid artery) or the distal transverse arch (between the left carotid artery and left subclavian artery). Although few data exist regarding stent angioplasty within the distal transverse aortic arch, general experience has been that this is a safe and effective procedure.⁹ For this intervention, an additional 4-Fr sheath is placed in the right radial artery, and a 4-Fr pigtail is advanced to the ascending aorta for angiography to assess appropriate stent position in relation to the origin of the left carotid artery and left subclavian artery.

Balloon Stent Angioplasty

Transcatheter stent angioplasty for postoperative recoarctation or native CoA at the isthmus has been demonstrated to be safe and effective.¹ The technique usually involves a femoral arterial approach. The exchange length wire is placed in the ascending aorta or subclavian artery.

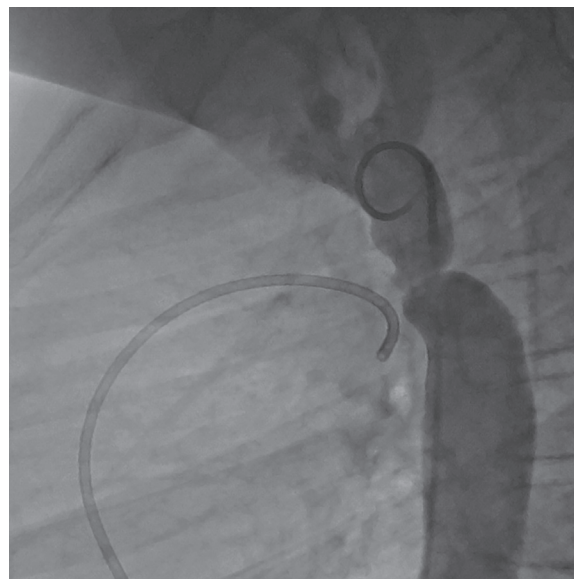


FIGURE 37.5 Aortic cineangiogram of recurrent coarctation of the aorta at the aortic isthmus.



FIGURE 37.6 Balloon stent angioplasty for aortic coarctation.

A high-pressure angioplasty balloon is used that is equal to or less than the diameter of the normal aortic segments around the stenosis (distal transverse arch, isthmus, or proximal descending aorta) or the diameter of the descending thoracic aorta near the diaphragm. The stent is mounted on the angioplasty balloon, and a sheath at least 1 to 2 Fr larger than that required by the angioplasty balloon is used. The stent length is dependent on the lesion length but is usually at least 35 to 50 mm. Intravascular ultrasonography is useful in ensuring that there is adequate apposition of the stent against the aortic wall. The stent is most often fully dilated (Figure 37.6 and Video 37.6), but for resistant lesions, it can be dilated over two procedures with 6 to 12 months between dilations. The

intervention is deemed successful with reduction in the peak-to-peak gradient to less than 3 mm Hg.⁹

A multicenter retrospective cohort study¹⁰ regarding transcatheter stent angioplasty for coarctation in patients with Turner syndrome has demonstrated that extreme care and vigilance are needed to manage this high-risk patient population. In this study, van den Hoven et al.¹⁰ included 19 patients; 3 (15.8%) had an adverse event, including 2 with aortic dissection despite use of covered stents. The authors concluded that coarctation intervention for patients with Turner syndrome is effective, but alternative treatment options should be carefully considered.

The COAST (Coarctation of the Aorta Stent Trial) trial¹¹ demonstrated that bare-metal stent (BMS) angioplasty for aortic coarctation reduced the proportion of patients with serious adverse events compared with surgical intervention (B Braun). In addition, BMS angioplasty for aortic coarctation also resulted in the reduction in the proportion of patients with postprocedure paradoxical hypertension compared with surgical patients. Consequently, the CP Stent and Mounted CP Stent are now indicated for use in the treatment of native or recurrent CoA involving a compliant aortic isthmus or first segment of the descending aorta where there is adequate size and patency of at least one femoral artery and the balloon angioplasty is contraindicated or predicted to be ineffective.

The COAST II trial¹¹ demonstrated that covered stent angioplasty for aortic coarctation reduces the proportion of patients with a serious adverse event attributed to the stent or procedure compared with surgery (B Braun). There were no uncontained aortic tears or large aneurysms or pseudoaneurysms, and all new aortic wall injuries were successfully repaired by covered stent implantation.

Despite this technology, late postcoarctation aneurysm formation remains a concern after balloon stent angioplasty for native or recurrent coarctation, resulting in the recommendation to perform aortic imaging within 12 to 18 months of the aortic intervention.¹² Primary covered stent angioplasty (Figure 37.7 and Video 37.7) should be considered for

patients with a genetic syndrome, existing aortic wall injury or wall injury noted after stent angioplasty, or age older than 40 years.

The NuDEL-CP premounted covered stent delivery system (B Braun) is approved for primary treatment of CoA as well as secondary treatment of aortic disrapture identified during angioplasty.¹³ This Gore-Tex-covered balloon-expandable stent is available premounted on a balloon in balloon within a 14- to 16-Fr delivery sheath allowing rapid placement during urgent situations. If an aortic diameter greater than 24 mm is necessary, 10 Zig CP covered stent (B Braun) are available.¹³

Endovascular Self-Expanding Stent Grafts

Endovascular self-expanding stent grafts have recently been reported for repair of CoA. In 2017, Zeinali et al.¹⁴ reported 62 adult patients who underwent stent implantation with self-expandable stents between 2005 and 2014. All procedures were successful with stent misplacement in 3 each managed with a second stent. With a mean follow-up period of 45 months, there were no aneurysms or stent fractures identified, but 3 patients had recoarctation with 2 managed with reintervention using balloon stent angioplasty.

Pulmonary Valve Replacement

Overview

Right ventricular (RV) outflow tract (RVOT) malfunction manifests as obstruction with RV hypertension, regurgitation with RV enlargement, or mixed disease. These derangements are common for patients with ACHD with tetralogy of Fallot, double-outlet right ventricle, pulmonary valve atresia, truncus arteriosus, or aortic valve disease after a Ross operation.¹ This RVOT malfunction can involve the native RVOT or occur after RV-to-PA conduit or a bioprosthetic pulmonary valve.

Cardiac MRI (CMR) has been used to determine timing of intervention based on RV ejection fraction, RV volume, and degree of pulmonary regurgitation. Currently, surgical intervention is indicated with indexed right ventricular end-diastolic volumes (RVEDV) greater than 150 mL/m² based on recently published data because studies have suggested an indexed RVEDV that exceeds 150 mL/m² may lead to irreversible RV dilation.¹

Transcatheter pulmonary valve replacement has evolved into a viable alternative to surgical conduit or bioprosthetic valve replacement.¹ This procedure has paved the way for a more advanced approach to congenital and structural interventional cardiology. Although many successes have been noted, challenges with this procedure include 18- to 24-Fr delivery systems, the need for a “landing zone” for the valve as well as pretesting, optimal timing for intervening to prevent RV dysfunction, and atrial or ventricular arrhythmias.

The procedure is performed under general endotracheal anesthesia, and access is usually obtained from the femoral vein; however, the procedure may also be performed via the internal jugular veins. After obtaining access, the patient is given intravenous heparin targeting an ACT greater than 250 seconds. Standard right heart catheterization is performed to assess the preprocedural saturations, pressures,

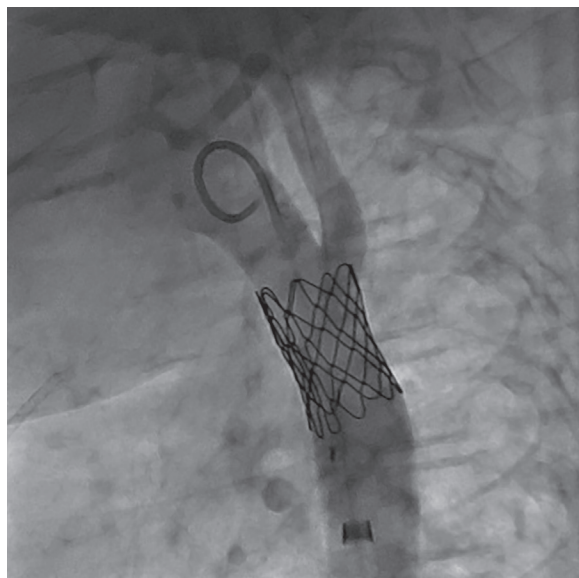


FIGURE 37.7 Balloon-covered stent angioplasty for aortic coarctation.

and the pressure gradient across the dysfunctional conduit. Angiography is then performed as follows: straight lateral and frontal with 20- to 30-degree cranial. Selective coronary angiography is performed simultaneously with a noncompliant angioplasty balloon (>8–10 atm) in the RVOT conduit. Adequate angiographic distance (at least 10 mm) from the edge of the inflated balloon to the origin of the left coronary artery must exist to place the valve safely without compression of the coronary arteries. Angiographic assessment of the RVOT size, anatomy, and RV function is of paramount importance to ensure appropriate valve delivery is feasible. Prestenting of the RVOT with a BMS before valve delivery is standard to reduce stent valve fracture when implanting the Melody valve.

The BMS is deployed on a balloon catheter over a stiff guidewire such as the Meier wire (Boston Scientific Corporation,) or Lunderquist wire (Cook Medical) curled in the distal pulmonary artery. Angiograms are performed before balloon inflation to ensure proper position for the stent (Figure 37.8 and Video 37.8).

Transcatheter Pulmonary Stent Valves

The Melody valve (Medtronic) is a bovine jugular vein valve creating compliant and flexible leaflets. It is sewn into a platinum iridium stent and preserved in a proprietary sterilant of glutaraldehyde and alcohol.¹⁵ The valve comes in one size (diameter, 18 mm; length, 28 mm) that is crimped to 6 mm and reexpanded up to 22 to 24 mm. The Medtronic Ensemble delivery system (Medtronic) consists of a delivery sheath with a balloon-in-balloon catheter onto which the valve is front loaded and crimped. The polytetrafluoroethylene (PTFE) sheath, which covers the valve during delivery, is withdrawn before deployment. Three sizes of the outer balloon are available: 18, 20, and 22 mm (Figure 37.9 and Video 37.9). Clinical studies have reported that this procedure is safe and effective in eliminating pulmonary outflow stenosis or regurgitation and reducing the indexed RV volumes as well as improving patients' New York Heart Association (NYHA) functional

class.¹ In addition, a multicenter prospective US clinical trial demonstrated freedom from Melody valve dysfunction or reintervention of 95.4% (124 of 136 patients) at 1 year of follow-up with a high rate of procedural success and improvement in NYHA functional class.¹⁵

The COMPASSION S3 (Congenital Multicenter trial of pulmonic valve dysfunction studying the SAPIEN 3 interventional transcatheter heart valve) trial recently reported using the SAPIEN 3 transcatheter heart valve (Edwards Lifesciences) for pulmonary valve replacement.¹⁶ The SAPIEN 3 is produced from three equal-sized bovine pericardial leaflets that are handsewn to a cobalt chromium alloy balloon-expandable stent with a polyethylene terephthalate outer skirt (Figure 37.10 and Video 37.10). The valve is preserved in low-concentration solutions of buffered glutaraldehyde and is processed with the Edwards Thermafix anticalcification pretreatment that is also used in the Carpentier-Edwards PERIMOUNT Magna surgical valve. This process involves heat treatment of the tissue in glutaraldehyde and uses ethanol and polysorbate-80. The valve is available in 20-, 23-, 26-, and 29-mm sizes and is mounted on a 3-cm-length volume-expansion balloon. A crimper is used to symmetrically crimp the valve onto the delivery catheter. The delivery system, Novoflex catheter (Edwards Lifesciences), decreases the required sheath size by then loading the valve onto the balloon inside the patient.

Although the SAPIEN3 transcatheter heart valve is available in larger sizes and shorter heights appropriate for larger conduits and challenging anatomy, it has a larger delivery system compared with the Melody valve that may render it more difficult to deliver. Also, the SAPIEN transcatheter heart valve system does not use a covering sheath; therefore, when it exits its delivery sheath (35 cm long), it may be difficult to retract inside the sheath. On the other hand, the Melody system is less bulky, and its retractable sheath protects the valve until it is deployed, but its limitation to 22 to 24 mm makes it less valuable for those with larger conduits.

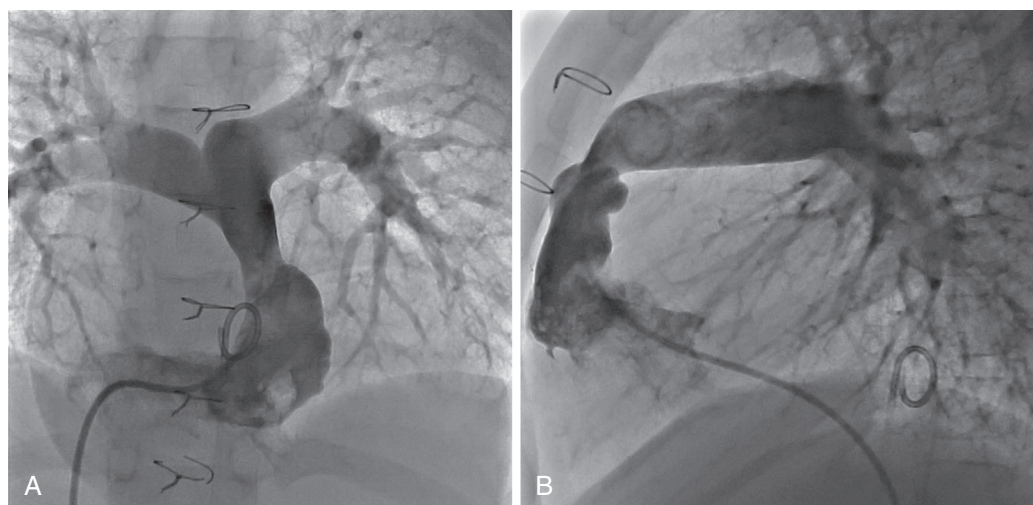


FIGURE 37.8 Right ventricular outflow angiogram using a 5-Fr pigtail catheter in the pulmonary artery cranial (A) and lateral (B) projections before transcatheter pulmonary valve replacement.

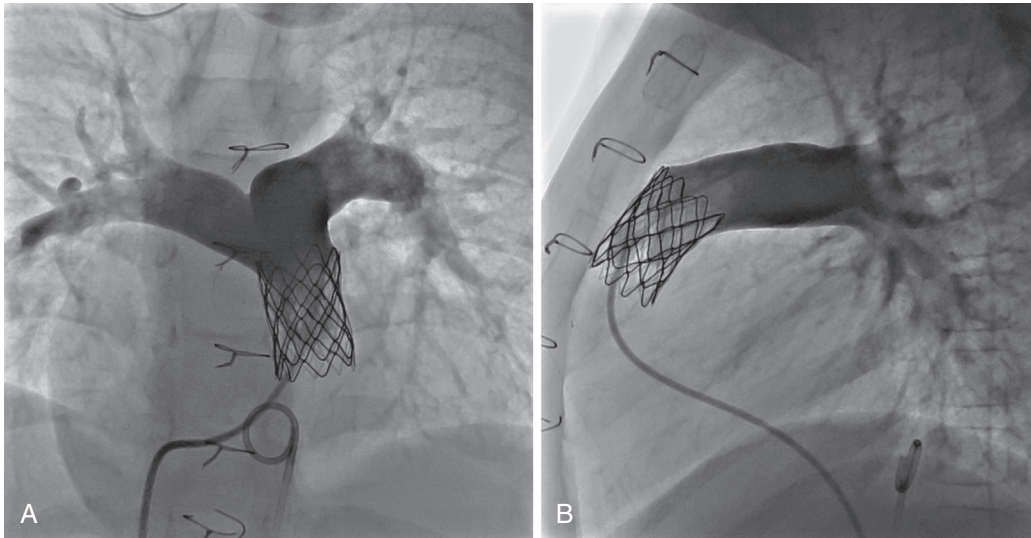


FIGURE 37.9 Prentest and Melody Valve deployment in the cranial (A) and lateral (B) projections.

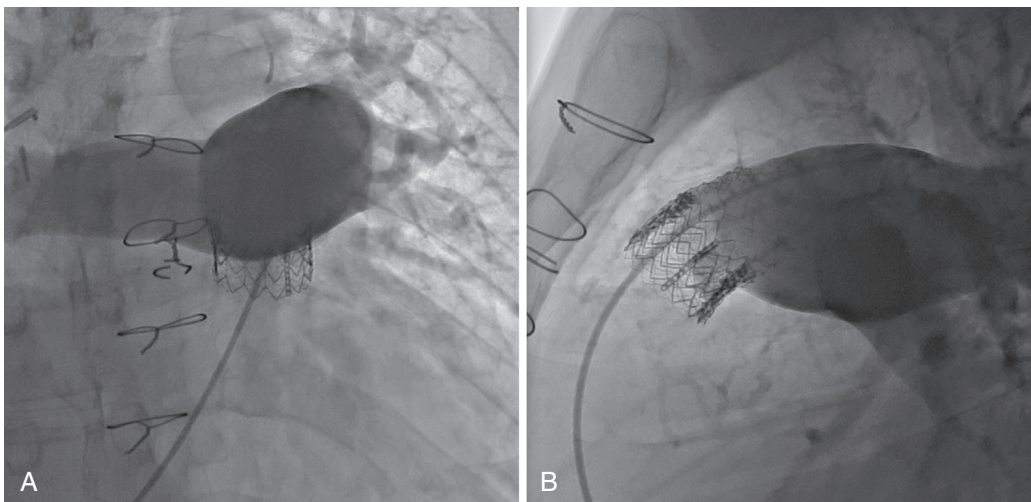


FIGURE 37.10 Prentest and SAPIEN 3 Valve deployment in the cranial (A) and lateral (B) projections.

The Alterra Adaptive Prentest (Edwards Lifesciences) is a self-expanding device made of nitinol and partially covered with expanded PTFE.¹⁷ This comes loaded within a delivery system and uses a control wheel to slowly retract the sheath. A 2020 report by Shahanavaz et al.¹⁷ involved 15 patients successfully implanted with a mean age of 20 years and RVOT diameters 27 to 38 mm with a length greater than 35 mm. After being deployed in the RVOT, this prentest is used immediately as a “landing zone” for the 29-mm SAPIEN3 transcatheter heart valve (Edwards Lifesciences).

The Harmony transcatheter pulmonary valve (TPV) (Medtronic) is used for nonsurgical replacement of an enlarged native RVOT.¹⁸ The Harmony TPV is a self-expanding porcine pericardium valve treated with α -amino oleic acid to mitigate leaflet calcification and a 0.2% glutaraldehyde sterilant. The valve is sutured within a nitinol frame sewn onto a polyester fabric tube 5.5 cm in length with an inflow diameter of 42 mm and outflow diameter of 34 mm. The

delivery system is a 25-Fr coil-loading catheter with an integrated retractable sheath to control self-expansion of the valve during deployment (Figure 37.11 and Video 37.11). A nonrandomized, prospective feasibility trial enrolled 66 participants for precatheterization assessment of the RVOT by CT angiography.¹⁸ Of these, 21 met criteria, 20 proceeded for implant, and 19 had successful Harmony valve placement. Of these 20 participants, 2 underwent early explant, and 17 completed 3-year follow-up¹⁸ with 1 having mild pulmonary valve regurgitation and the remainder none or trace. At 3-year follow-up, the mean RVOT gradient was 15.7 ± 5.5 mm Hg, and there were no late frame fractures or erosions. Two participants had an increasing gradient across the RVOT noted by CT to be neointimal ingrowth and were successfully revised with a Melody valve-in-valve transcatheter.

After this procedure, hemostasis is achieved with either Perclose sutures (Abbott Vascular) that are inserted before the large sheath (preclose) or by a figure-of-8 suturing

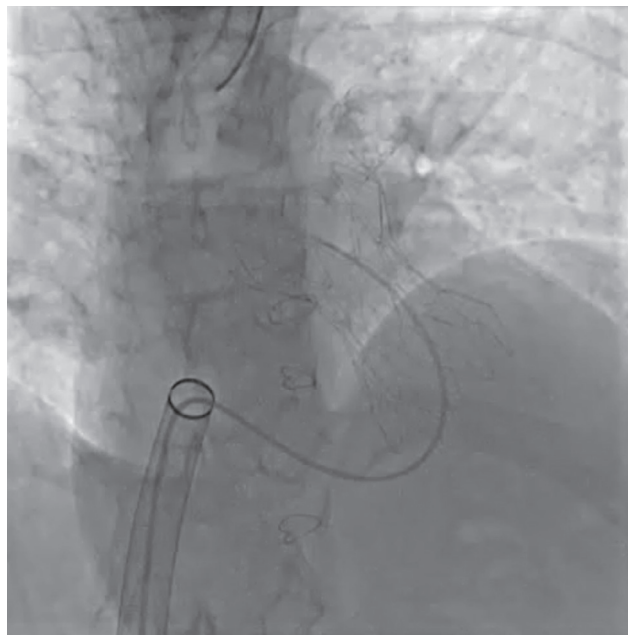


FIGURE 37.11 Harmony valve deployment for transcatheter pulmonary valve replacement.

technique. The patient is admitted for observation overnight. Complete physical examination, electrocardiography, chest radiography, and echocardiography are performed before patient discharge. Aspirin 81 mg is advised for at least 3 to 6 months. Follow-up outpatient visits are recommended at 1, 6, and 12 months and yearly thereafter. Chest radiography is obtained at 6 months to look for valve and stent positions and any potential stent fracture. Echocardiography is routinely used to evaluate RV function, regurgitation, and stenosis with each visit. CT or CMR is also part of follow-up protocol.

Conduit rupture has also been reported.¹ Risk factors have yet to be fully elucidated. Increasingly, covered stents are being used with aggressive prestenosing of heavily calcified conduits. In the event of conduit rupture, self-expanding stents have been used to create a seal and prevent further risk of bleeding.¹

Valve-in-valve transcatheter pulmonary valve replacement has been performed to treat patients with the Hammock effect, stent fractures, and residual stenosis. It has been noted that repeat transcatheter pulmonary valve replacement has resulted in freedom from surgical reintervention, including intentional fracture of the existing bioprosthetic ring.¹⁹ When appropriate, this approach should be considered an alternative to surgery because using this management strategy may indefinitely halt the need for surgical reintervention.

Endocarditis remains rare. The culprit organisms reported include *Staphylococcus aureus*, *Streptococcus* spp., and *Candida albicans* in patients with compromised immunity.¹ American Heart Association subacute bacterial endocarditis guidelines recommend prophylaxis for patients with a bioprosthetic valve.

Research is ongoing to broaden the use of this technology when treating patients with dilated RV dysfunction. In addition, affordability is an important factor that must be considered.

CONCLUSIONS

Congenital heart disease in the adult population, more than any other cardiovascular condition, is outgrowing the current medical facilities established to care for them. With better surgical options during childhood, most of these patients are entering adulthood with needs for ongoing medical care. Most interventions are rarely curative; thus, a lifetime of care is required. Clinical systems designed for the transition of these patients out of pediatric clinics, where many continue to receive their care, and into organized, regional ACHD centers of excellence will facilitate this process. As the catheter-based technology continues to advance regarding congenital heart disease, more and more patients will be coming to the catheterization laboratory for palliative interventions such as device deployment or stent valve angioplasty.²⁰

Cardiac catheterization for congenital heart disease has evolved from its early days as an exclusively diagnostic tool to a dynamic and continuously growing field of therapeutic interventional procedures for children and adults with cardiac abnormalities. The physicians and industry have a history of working together to push the field forward, finding novel solutions to difficult problems while making the products to accomplish these goals smaller and safer. Interventional cardiologists and cardiothoracic surgeons have truly become an organized team in the treatment of once uniformly fatal conditions to offer longer and better quality of life to a diverse group of complex and rewarding patients.

This chapter has summarized some of the interventional techniques used in the catheterization laboratories in congenital heart disease. Treating adults with congenital heart disease is a growing field and requires skilled personnel trained in both adult diseases and congenital heart disease to be able to understand the physiology and the anatomy of the cardiac lesions and hence the ability to intervene.

The practice of interventional cardiology in adults with ACHD requires special training and fully equipped catheterization laboratories to help minimize the risks of such procedures.²⁰ Surgical back-up is crucial in all institutions practicing congenital cardiac intervention. Last, cardiac intervention is a rapidly growing and expanding field that now involves at its far end percutaneous valve placement and repair. The near future will bring further advances in this field.

REFERENCES

1. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73(12):1494-1563.
2. Papamichalis M, Xanthopoulos A, Papamichalis P, Skoularigis J, Triposkiadis F. Adult congenital heart disease with pulmonary arterial hypertension: mechanisms and management. *Heart Fail Rev*. 2020;25(5):773-794.
3. Gal   N, Humbert M, Vachiery J-L, et al. 2015 ESC/ ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67-119.

4. Schuijt MTU, Blok IM, Zwinderman AH, et al. Mortality in pulmonary arterial hypertension due to congenital heart disease: serial changes improve prognostication. *Int J Cardiol.* 2017;243:449-453.
5. Rajeshkumar R, Pavithran S, Sivakumar K, Vettukattil JJ. Atrial septostomy with a predefined diameter using a novel Occlutech atrial flow regulator improves symptoms and cardiac index in patients with severe pulmonary arterial hypertension. *Catheter Cardiovasc Interv.* 2017;90(7):1145-1153.
6. Al-Hijji M, Sabbagh AE, Hajj SE, et al. Coronary artery fistulas: indications, technique, outcomes, and complications of transcatheter fistula closure. *JACC Cardiovasc Interv.* 2021;14(13):1393-1406.
7. Saboo SS, Chamrath M, Bhalla S, et al. Pulmonary arteriovenous malformations: diagnosis. *Cardiovasc Diagn Ther.* 2018;8(3):325-337.
8. Kramdhari H, Valakkada J, Ayyappan A. Diagnosis and endovascular management of pulmonary arteriovenous malformations. *Br J Radiol.* 2021;94(1123):20200695.
9. Agasthi P, Pujari SH, Tseng A, et al. Management of adults with coarctation of aorta. *World J Cardiol.* 2020;12(5):167-191.
10. Van den Hoven AT, Duijnhouwer AL, Eicken A, et al. Adverse outcome of coarctation stenting in patients with Turner syndrome. *Catheter Cardiovasc Interv.* 2017;89:280-287.
11. Ringel RE, Vincent J, Jenkins KJ, et al. Acute outcome of stent therapy for coarctation of the aorta: results of the coarctation of the aorta stent trial. *Catheter Cardiovasc Interv.* 2013;82(4):503-510.
12. Tretter JT, Jones TK, McElhinney DB. Aortic wall injury related to endovascular therapy for aortic coarctation. *Circ Cardiovasc Interv.* 2015;8:e002840.
13. Morgan GJ, Kenny D, Duke C, Walsh KP, Qureshi SA. Initial assessment of a novel delivery system (NuDEL) for the covered Cheatham-Platinum stent. *Cardiol Young.* 2017;27(8):1465-1469.
14. Zeinali AMH, Sadeghian M, Qureshi SA, Ghazi P. Midterm to long-term safety and efficacy of self-expandable nitinol stent implantation for coarctation of aorta in adults. *Catheter Cardiovasc Interv.* 2017;90(3):425-431.
15. Jones TK, McElhinney DB, Vincent JA, et al. Long-term outcomes after Melody transcatheter pulmonary valve replacement in the US Investigational Device Exemption Trial. *Circ Cardiovasc Interv.* 2022;15:e010852.
16. Sinha S, Aboulhosn J, Asnes J, et al. Initial results from the off-label use of the SAPIEN S3 valve for percutaneous transcatheter pulmonary valve replacement: a multi-institutional experience. *Catheter Cardiovasc Interv.* 2019;93(3):455-463.
17. Shahanavaz S, Balzer D, Babaliaros V, et al. Alterra Adaptive Prestent and SAPIEN 3 THV for congenital pulmonic valve Dysfunction: an early feasibility study. *J Am Coll Cardiol Interv.* 2020;13(21):2510-2524.
18. Benson LN, Gillespie MJ, Bergersen L, et al. Three-year outcomes for the Harmony native outflow tract early feasibility study. *Circ Cardiovasc Interv.* 2020;13:e008320.
19. Shahanavaz S, Asnes JD, Grohmann J, et al. Intentional fracture of bioprosthetic valve frames in patients undergoing valve-in-valve transcatheter pulmonary valve replacement. *Circ Cardiovasc Interv.* 2018;11:e006453.
20. Aboulhosn JA, Hijazi ZM, Kavinsky CJ, et al. SCAI position statement on adult congenital cardiac interventional training, competencies and organizational recommendations. *Catheter Cardiovasc Interv.* 2020;96:643-650.

